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LOCALIZING VALUE OF VISUAL FIELDS IN PATIENTS WITH EARLY CHIASMAL LESIONS

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PHILADELPHIA

THE MAJORITY of patients operated on for tumors in the neighborhood of the chiasm give a history of visual difficulty as their first noticeable complaint. In most cases the patient states that he noticed diminished vision of one eye coming on slowly, for which an oculist or an optometrist was consulted, and that numerous prescriptions for glasses were given without any benefit. The patient frequently states that he went from one eye specialist to another over a period of months, or even years, before some one finally took his visual fields and told him that something was pressing on his visual pathway and referred him to a neurosurgeon for diagnosis and treatment.

The history may also reveal that during this period the patient began to have headaches and various structural and physiologic abnormalities suggestive of pituitary dysfunction, but these symptoms are invariably not his chief complaint and are brought out only by careful questioning. Emphasis is nearly always laid on the disturbance in vision. This may be either a loss of central visual acuity or a noticeable contraction of half the visual field or both. The ophthalmologist is the one, therefore, who is directly responsible for the early diagnosis in these cases. The diagnosis can be made, or at least suggested, only by the changes in the visual fields. If peripheral fields alone are taken, the diagnosis will frequently be missed in the early stages, as only the central isopters show the earliest changes. Both central and peripheral isopters are necessary for the evaluation of the fields. Even with careful field studies, the diagnosis can be missed if one is not constantly alert to the fact that the fields may be atypical in the early stages and may not show characteristic signs of chiasmal interference, that is, bitemporal or homonymous hemianopsia.

From the Departments of Ophthalmology and Neuro-Surgery of the Hospital of the University of Pennsylvania.

One of the patients reported on here (case 3) had a craniopharyngioma which was missed by one of us (F. H. A.), even though the fields were taken, because these studies showed only very early changes in the field of one eye when she was first examined.

In addition to their diagnostic value, visual fields taken early in the course of a chiasmal lesion should be of aid to the neurosurgeon in localizing the tumor in respect to the chiasm. Whenever possible, most neurosurgeons prefer to operate on the right side of the head for tumors in this neighborhood in order to avoid the speech center on the left side in right-handed people. This rule is broken, however, if the vision in one eye is very much worse than that in the other. In this case, it is preferred to make the approach on the side with the poorer vision. The roentgenographic findings may also help in the location of the lesion, but frequently they do not. It would be helpful to the surgeon if he could predict with reasonable accuracy on which side of the chiasm the tumor is situated—whether it is lateral, anterior or posterior, or whether it is coming directly up from below. It is reasonable to expect that some information could be derived from an analysis of the early field changes as to the direction from which a lesion is attacking the chiasm. Such information would also be suggestive of the nature of the lesion, that is, whether it is an intrasellar adenoma, a craniopharyngioma, a suprasellar meningioma or an aneurysm.

It is the experience of most authors that the late field changes have little localizing value. Traquair [1] stated:

> Too much reliance should not be placed on the inferences from the field changes as to the exact site or position of a tumor or other lesion, though on the whole they may be regarded as a trustworthy guide to the point at which the nerve fibers are affected.

Many examples could be cited from the literature which demonstrate that one must be guarded against too positive a statement as to the localizing value of the fields. In speaking of the effects of pressure on the optic nerves themselves, for example, McConnell and Mooney [2] stated that loss of the lower nasal quadrants of the visual fields does not necessarily imply that the upper surfaces of the optic nerves are being pressed on. This has also been our experience (case 9). In several cases the optic nerves or tracts were found to be grooved by blood vessels at operation without any corresponding defects in the visual fields having been found prior to operation. On the other hand, a recent report of a case of suprasellar meningioma by Mathewson [3] indicates that in selected cases the early field changes may have definite

1. Traquair, H. M.: Introduction to Clinical Perimetry, ed. 4, London, Henry Kimpton, 1942, p. 229.

2. McConnell, A. A., and Mooney, A. J.: Brain **61**:37, 1938.

3. Mathewson, W. R.: Brit. J. Ophth. **30**:92, 1946.

localizing value. Kestenbaum [4] reviewed the various types of chiasmal lesions and indicated the type of field change which should occur in lesions approaching the chiasm from different positions. We are not aware of any analysis having been made of a series of cases of verified chiasmal lesions for the purpose of determining how well one can predict the location of a lesion from the character of the early visual fields.

The present paper is a report of a series of cases in which the visual fields taken preoperatively were analyzed and the site of the tumor predicted on this basis alone, without knowledge of the operative findings. The theoretic location of the tumor was then compared with that described in the operative notes. All the cases are from the neurosurgical service of one of us (F. C. G.) in the Hospital of the University of Pennsylvania. Most of the fields were taken in the department of ophthalmology of the University Hospital. Only those cases were used in which the visual fields were taken early enough before operation to give a clue to the possible site of interference. In this way all cases were ruled out in which the defect had reached the stage of complete bitemporal hemianopsia. It should also be emphasized that all the cases were selected from the file of lesions around the chiasm. The interpretation of the fields was therefore made with the knowledge that the tumor was a chiasmal one.

The peculiar distribution of the nerve fibers in the chiasm should enable one to predict the situation of a growing tumor with some degree of accuracy, depending on where the tumor comes into contact with the chiasm. It is probable that the field changes are not due to direct pressure of the tumor on the nerve fibers, but depend rather on the shutting off of their blood supply, which causes an anoxia, preventing conduction in the fibers. This supposition is borne out by the rapidity with which the fields may return to normal after the pressure has been relieved by operation. It is common to find decided improvement, and even complete recovery, of the fields within several days of operation, a result which would not occur if the pressure had caused organic changes in the fibers.

Fibers from the upper half of each retina occupy the upper half of each optic nerve and run into the upper, or dorsal, part of the chiasm. Similarly, the fibers from the lower half of each retina are found in the lower half of each optic nerve and in the lower, or ventral, part of the chiasm. The chiasm can be thought of as made up of three layers of fibers: a lower, or most ventral; a middle, and, finally, an upper, or dorsal, layer. The uncrossed temporal fibers remain on the outside,

4. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1947.

or temporal, surface of the chiasm. The fibers from each inferior temporal retinal quadrant run on the extreme outside, or lateral edge, of the chiasm and occupy the middle layer. The uncrossed fibers from each upper temporal retinal quadrant run nearer the midline and almost entirely in the upper, or dorsal, layer. The fibers from the inferior nasal retinal quadrant are found almost entirely in the lower, or most ventral, layer. These fibers lie in the anterior portion of the chiasm, and the most anterior of these swing forward into the opposite optic nerve to form the anterior knee. The fibers from the upper nasal retinal quadrant run backward almost into the optic tract on the same side before swinging across the chiasm into the opposite optic tract, skirting the posterior surface of the chiasm and eventually lying on the mesial side of the tract near its surface. They comprise the middle and uppermost layers of fibers. From this description, it is obvious that the lower layer of the chiasm is formed almost entirely of the crossing fibers from each inferior nasal retinal quadrant. These are the fibers which form the anterior knee in each optic nerve. The middle layer of the chiasm contains both crossing and noncrossing fibers, i. e., the crossing fibers from each superior nasal retinal quadrant and the noncrossing fibers from each superior temporal retinal quadrant. The upper layer is formed by both crossing and noncrossing fibers, i. e., those from the superior nasal retinal quadrant and the fibers from the superior temporal retinal quadrant. While this relationship may seem to be complex, Kestenbaum has considerably simplified it by pointing out that the result is, in general, what would be obtained by a rotation of the optic nerve around its anteroposterior axis 45 degrees toward each nasal side.

The macular fibers form a separate bundle throughout the chiasm, coming from the middle of the optic nerve as they enter the chiasm. The uncrossed temporal fibers go directly down the side of the chiasm, about equidistant from its lateral surface, to enter the tract on the same side at about its middle. The crossing macular fibers go to the posterior part of the chiasm before they cross to the opposite side, so that the actual crossing lies close to the posterior edge of the chiasm. In this situation they are in close vicinity to the third ventricle and, according to Kestenbaum, are separated from it only by Gudden's commissure. Figure 1 attempts to show the course of these fibers in a third dimensional drawing. The course of the fibers as outlined here is based largely on the work of Wilbrandt, and there has been little recent work of an anatomic nature which throws any further light on the arrangement of the fibers in the chiasm. Most of the evidence within recent years has come from an evaluation of clinical material. As Clark[5] pointed out,

5. Clark, W. E. L.: Physiol. Rev. **22**:209, 1942.

The intimate topographical relation between the optic chiasma and certain hypothalamic commissures in this region makes it very difficult in normal preparations to decipher the precise course of the retinal fibres here. . . . For one thing, the fibres of the supra-optic commissures (which probably have nothing to do with visual functions) are not always distinguishable from retinal fibres. Also, in the chiasma the decussating fibres may run an aberrant course which can be very misleading to the casual observer.

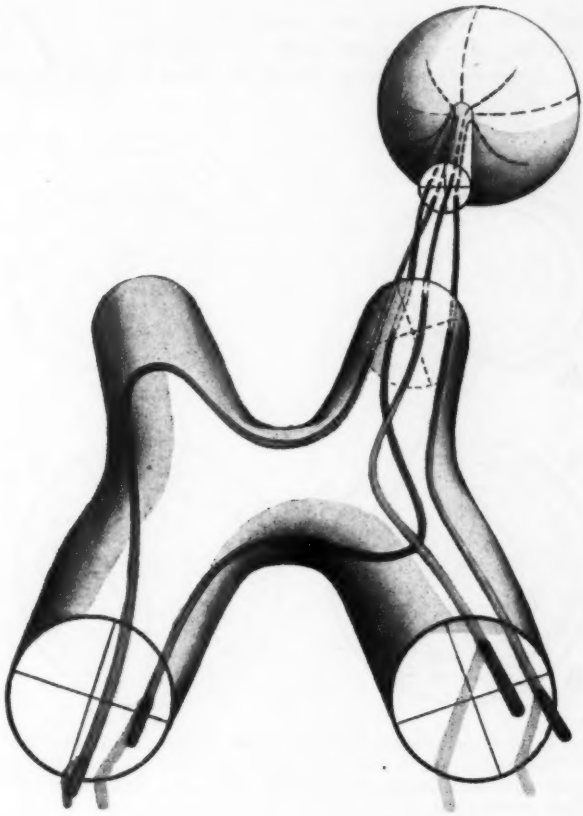

Fig. 1.—Arrangement of the fibers in the chiasm coming from the four quadrants of the retina as seen from the back of the eye.

1. The upper nasal quadrant of the retina sends fibers into the middle layer of the chiasm which form the posterior knee on the ipsilateral side before crossing over in the back of the chiasm.

2. The superior temporal quadrant sends fibers into the upper layer of the chiasm which form the portion of the uncrossed bundle nearest the midline.

3. The inferior temporal quadrant sends fibers into the middle layer of the chiasm which form the uncrossed bundle nearest the temporal surface of the chiasm.

4. The inferior nasal quadrant sends fibers in the lower layer of the chiasm which cross over at the anterior end of the chiasm to form the anterior knee.

REPORT OF CASES

CASE 1.—R. C., aged 40, was admitted to the neurosurgical service on Sept. 5, 1947.

He had a history of failing vision in the right eye for months. He had consulted an ophthalmologist, who found a scotoma for red in the right visual field and told the patient to stop smoking, which he did, without any improvement. He had no headaches or other symptoms. His family physician finally referred him to one of us (F. C. G.).

On his admission, vision with best correction was 6/30 in the right eye and 6/7.5 in the left eye. His peripheral fields for 1/330 white and 6/330 red were practically full. There was a contraction of the upper temporal quadrant in the

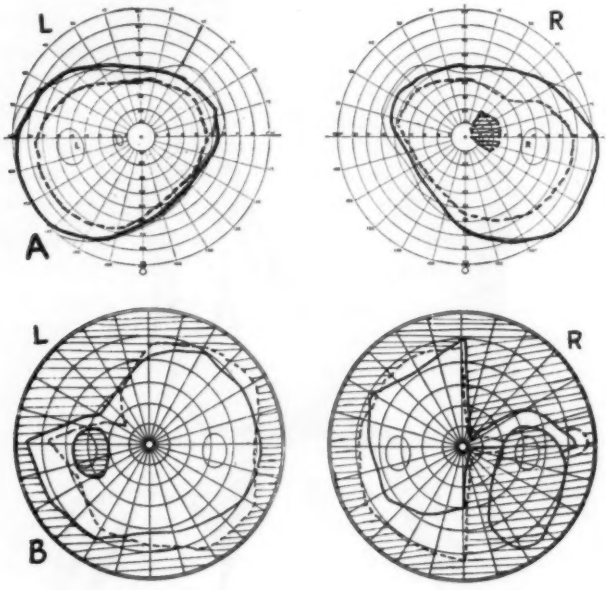

Fig. 2 (case 1).—*A*, peripheral fields to 1/330 white (solid line) and 5/330 red (broken line). The fields are full to 1/330 white. The right eye shows contraction of the upper temporal quadrant to 5/330 red and a scotoma to 5/330 red on the temporal side of fixation.

B, central fields, showing complete loss of the right temporal quadrant to 2/1,000 white and 10/1,000 red and loss of the left upper temporal quadrant to 2/1,000 white and 10/1,000 red.

right eye for 5/330 red and a scotoma for red on the temporal side of fixation in the right eye only. This was suggestive of a hemianopic scotoma. The central fields showed complete loss of the right temporal quadrant to 2/1,000 white and 10/1,000 red and loss of the left upper temporal quadrant to 2/1,000 white and 10/1,000 red (fig. 2 *A* and *B*).

An analysis of the fields placed the lesion under the anterior end of the chiasm on the right side, where the right optic nerve joins the chiasm (fig. 3).

Operative Notes (Dr. F. C. Grant).—"A right prefrontal craniotomy was performed. When the dura was opened, the right olfactory and right optic nerves

were seen, the latter humped up over a large, and what felt like a semicystic, tumor" (fig. 4).

The diagnosis was chromophobic adenoma of the pituitary gland.

Comment.—In this case the loss of the temporal field on the right side and of the upper temporal quadrant on the left side, together with loss of the crossing macular fibers on the right side, pointed to the location of the lesion and corresponded well with the situation found at operation.

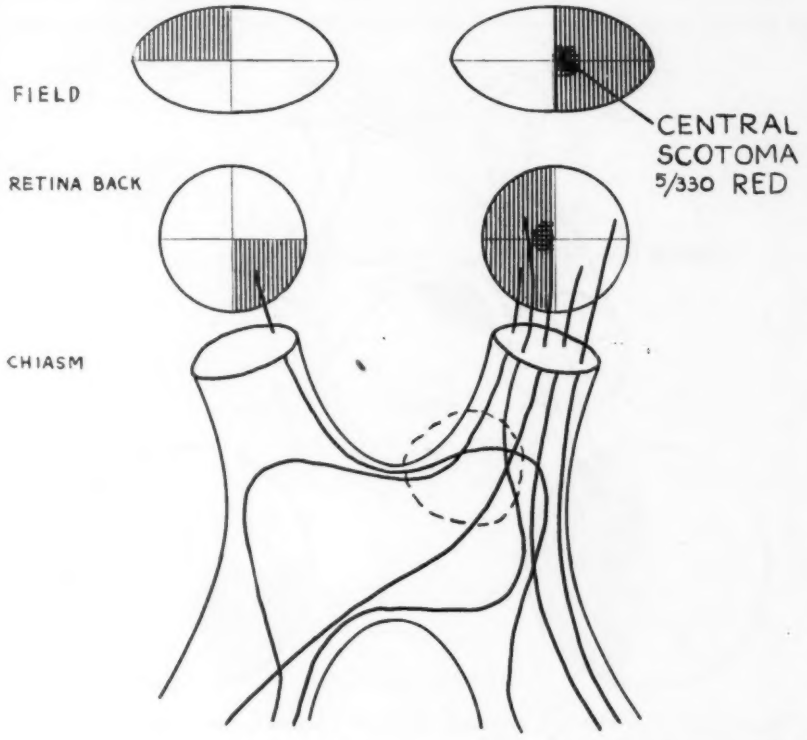

Fig. 3 (case 1).—Analysis of fields which placed the lesion under the front end of the chiasm on the right side where the right optic nerve joins the chiasm, catching fibers from the upper and lower nasal retinal quadrants on the right side and from the lower retinal quadrant on the left side.

CASE 2.—J. J., aged 36, was admitted to the neurosurgical service on March 22, 1943.

There was a history of poor vision for many years. He had been given numerous prescriptions for glasses by optometrists and ophthalmologists. One ophthalmologist found his disks pale and referred him to a neurologist, who gave him antisyphilitic treatment, despite a negative serologic reaction and a normal spinal fluid. He was then referred to the Wills Hospital, in 1940. At that time his peripheral fields showed a hemianopic scotoma to both white and color in the temporal half of each field. His visual acuity at that time was 6/10

in the right eye and 6/21 in the left eye with best correction. He was referred to Dr. Bernard Alpers for neurologic study, and a diagnosis of craniopharyngioma was made. He was eventually operated on (by Dr. Grant) on March 26, 1943.

Analysis of the early field changes of hemianopic central scotoma in each temporal field suggests a lesion pressing at the posterior end of the chiasm, catching the crossing macular fibers (fig. 5). From 1940 until operation, his fields showed an increasing loss of both upper and lower temporal quadrants until just prior to operation, when they showed a complete bitemporal hemianopsia to white, red and green.

Operative Notes (Dr. Grant).—"After a right transfrontal craniotomy, the dura was reflected from the right orbital plate and sectioned along the sphenoidal ridge.

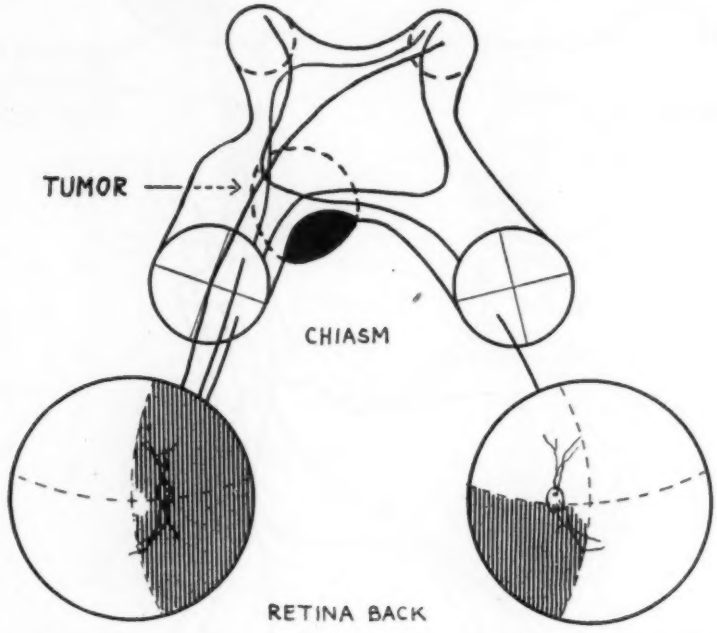

Fig. 4 (case 1).—Position of tumor found at operation under the front end of the chiasm on the right side.

This exposed the right optic nerve, which was tremendously distorted by a greenish tumor lying below and behind it. The tumor was thoroughly wrapped around the optic nerve and chiasm and extended well posteriorly. I thought I was able to see in front of the capsule into the sella, and possibly even to visualize the pituitary gland itself, lying in front of the anterior part of the tumor capsule."

The diagnosis was craniopharyngiomatous cyst.

Comment.—In this case the bitemporal hemianopic scotoma suggested a lesion pressing at the posterior end of the chiasm and corresponded well to the situation of the tumor found at operation. It also was suggestive of the nature of the tumor, a craniopharyngioma.

CASE 3.—Mrs. W. C., aged 45, was admitted to the neurosurgical service on Nov. 21, 1941.

In June 1940 she complained of failure of vision in the left eye. She had consulted several ophthalmologists, who told her that they could find nothing wrong with her eyes. She was seen in the office of one of us (F. H. A.) in July 1940. Visual acuity was 6/7.5 in each eye. This could not be improved. Ophthalmoscopic examination revealed normal fundi. The patient seemed to be highly neurotic; she was told that nothing abnormal could be found and was asked to return. Visual fields were not taken at this time. She returned in January

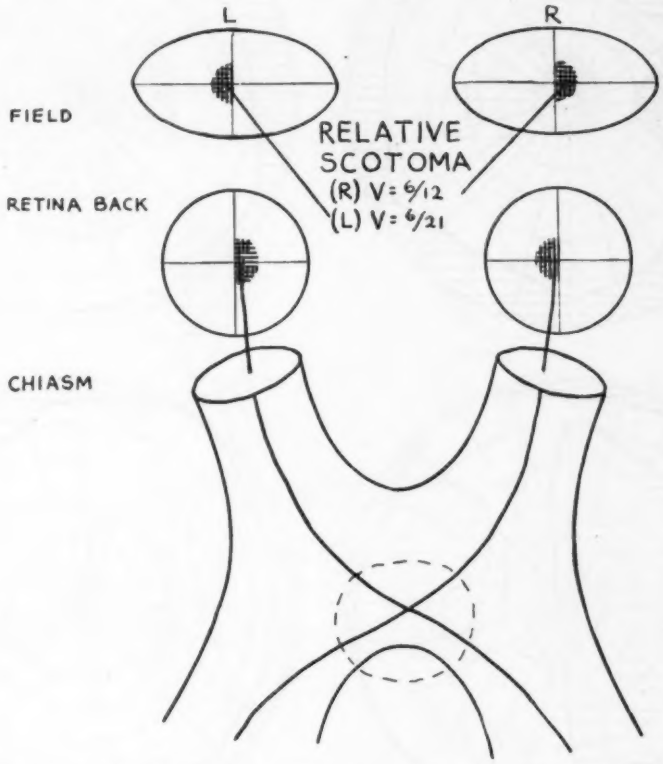

Fig. 5 (case 2).—Analysis of early changes in fields which showed a hemianopic central scotoma to 5/1,000 red. The position of the tumor was under the chiasm at the posterior end, catching crossing macular fibers.

1941, complaining of continued blurred vision in the left eye, which she said had become considerably worse. Her visual acuity was then 6/12 in the right eye and 6/150 in the left eye. This could not be improved with glasses. The fundi still showed no changes. Visual fields, which were then taken, showed a general contraction in the periphery of the right eye and approximately the same change in the left eye, but the loss was more marked in the upper temporal quadrant of the left eye. The central fields of the right eye were normal. The central fields of the left eye showed a slight cut in the upper temporal quadrant (fig. 6A). I wanted to use drops in her eyes and dilate her pupils, but she refused, saying

that her trouble had commenced when an ophthalmologist had put drops in her eyes. Accordingly, she left my office. The fields were not considered suggestive, and the cut in the upper temporal quadrant of the left eye was entirely overlooked. Nothing more was heard from her until she was reported as having entered Dr.

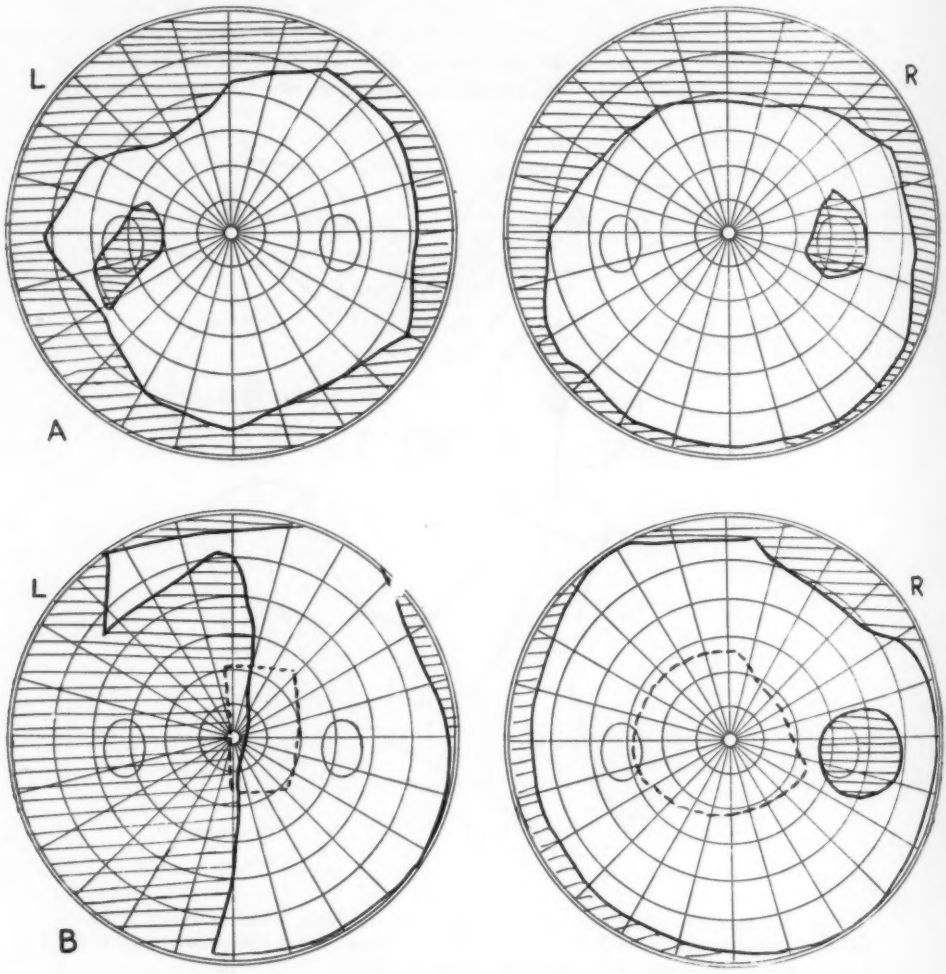

Fig. 6 (case 3).—*A*, central fields to 2/1,000 white, made on Jan. 24, 1941, showing cut in the upper temporal quadrant of the left field.

B, central fields to 1/1,000 white (solid line) and 3/1,000 red (broken line), made on Nov. 21, 1941, showing complete loss of the temporal field in the left eye and loss of the upper temporal quadrant in the right eye. Vision was 3/30 in the left eye and 6/12 in the right eye.

Grant's service on November 21, ten months later. She had been sent to Dr. Grant by another ophthalmologist, who two weeks previously had made a diagnosis of a tumor of the pituitary gland.

Fields which were taken in our outpatient department on Nov. 24 showed a definite upper temporal quadrant defect in the right eye and complete loss of the temporal field in the left eye (fig. 6*B*). Analysis of these fields indicates a tumor on the left side of the chiasm at its anterior part, catching both the upper and the lower nasal fibers of the left eye and the lower nasal fibers of the right eye (fig. 7). This case is similar to case 1 except that the tumor was on the opposite side.

Operative Notes.—"A left frontal craniotomy was performed. The dura was opened in the routine fashion and the left optic nerve exposed, revealing a tumor in the sella, which exerted pressure on the left optic nerve."

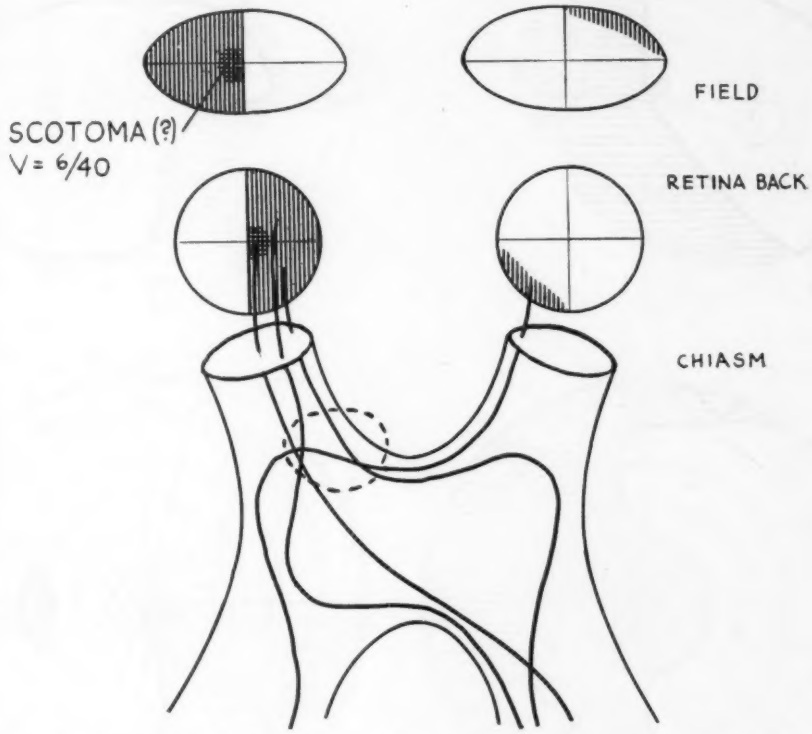

Fig. 7 (case 3).—Analysis of the fields, indicating a tumor on the left side of the chiasm underneath its anterior end, catching both the upper and the lower nasal fibers of the left eye and the lower nasal fibers of the right eye.

The diagnosis was eosinophilic adenoma of the pituitary gland.

Comment.—The diagnosis in this case was missed because of our failure to interpret the fields taken early in the course of the disease. It is certain that if the central fields had been taken with small colored test objects, characteristic fields would have been obtained. A year later the fields were unmistakable and localized the lesion in the place in which it was found at operation.

CASE 4.—K. B., aged 52, was admitted to the neurosurgical service on Sept. 17, 1947.

The patient had failing vision in the left eye for several years and glasses were changed repeatedly. In spite of this, her vision had continued to fail, and at the time of our examination her vision was very poor in the right eye

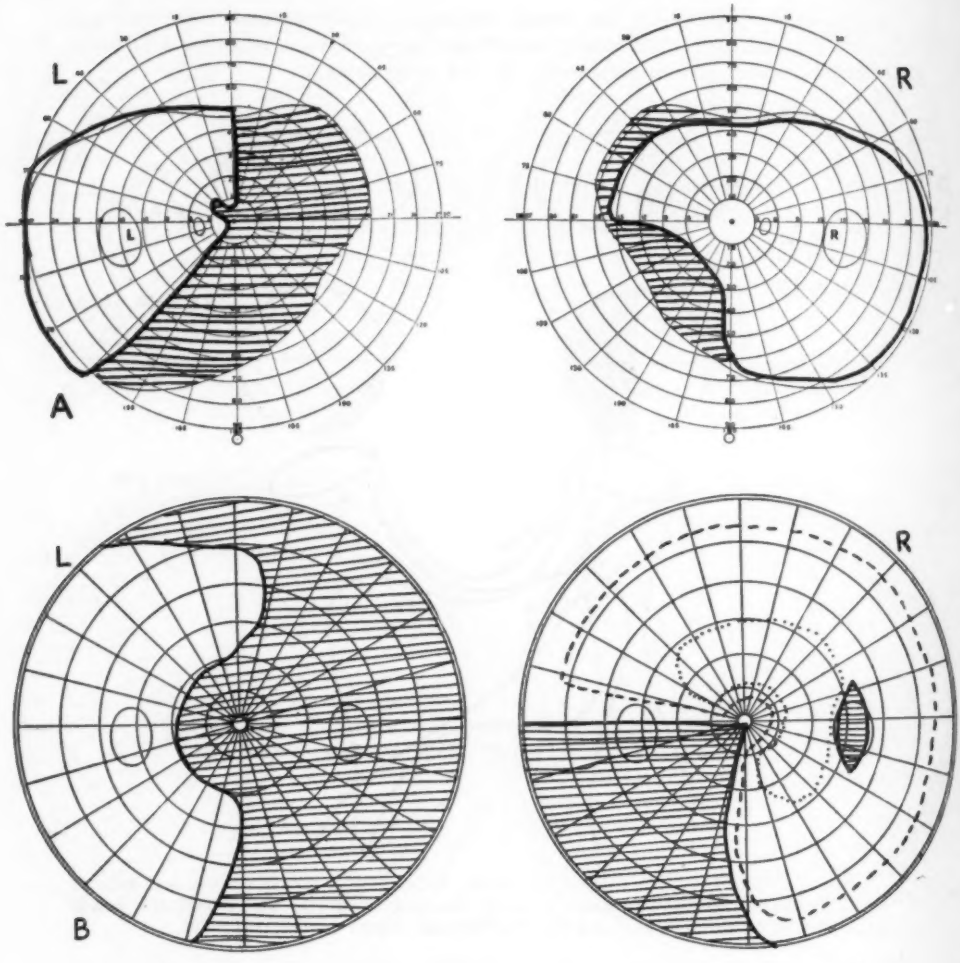

Fig. 8 (case 4).—*A*, peripheral fields to 10/330 white in the right eye and to 10/330 white in the left eye, made on Aug. 29, 1947.

B, central fields to 20/1,000 white (solid line), 5/1,000 white (broken line) and 3/1,000 white (dotted line), made on Aug. 29, 1947.

and practically gone in the left. She was seen two weeks prior to admission in our office by Dr. Harold G. Scheie. Her vision at that time was 6/120 in the right and was limited to hand movements in the left eye with best correction. Both optic nerve heads were pale, the left being more so than the right. Her

peripheral fields showed loss of the lower nasal quadrant in the right eye and complete loss of both nasal quadrants in the left eye, the defect extending into the lower temporal quadrant. Central fields bore this out along with the loss of the macular fibers in the left eye. Dr. Scheie made a diagnosis of bilateral primary optic nerve atrophy, more advanced in the left eye. He stated that because of the long history of loss of vision in the left eye, the most likely diagnosis was a neoplasm which caused the defect by direct pressure or by pressing the optic nerve laterally against the internal carotid arteries. He expressed the opinion that an aneurysm was possible and that basal arachnoiditis should be considered" (figs. 8 and 9).

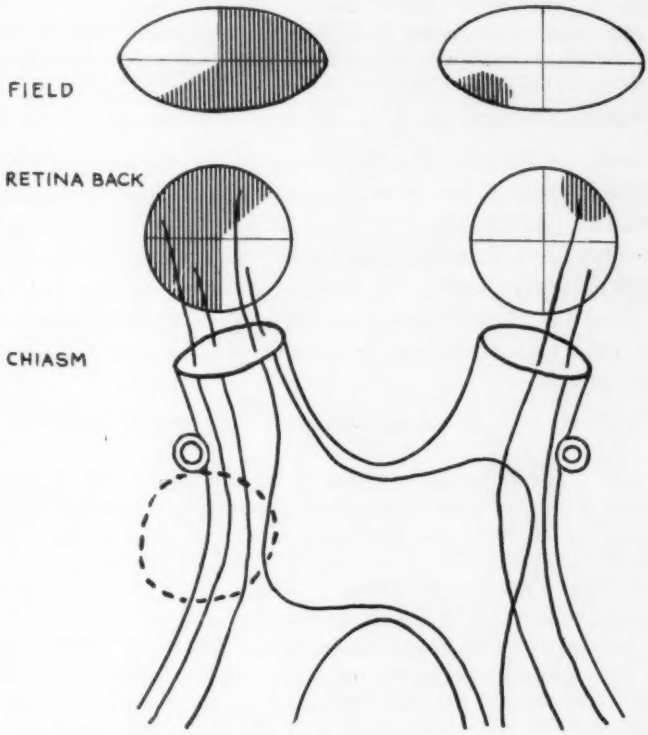

Fig. 9 (case 4).—Analysis of field defects indicating pressure on both sides of the chiasm in order to produce a binasal hemianopsia. The lesion is probably on the left side, pressing against the lateral aspect of the chiasm and pushing the chiasm over to the right, so that it presses against the right internal carotid artery or against the bony foramen. The fibers from the upper temporal quadrant on the right side, rather than those from the lower temporal quadrant, were pressed on. This may be due to the fact that the affected fibers lie in the upper part of the chiasm, where the artery comes in contact with the chiasm.

Analysis of the field defects indicates that pressure must have been present on both sides of the chiasm in order to produce binasal hemianopsia. The lesion was probably on the left side, pressing against the lateral aspect of the chiasm and pushing the chiasm over to the right, so that it pressed against the right internal carotid artery, or the right optic nerve pressed against the bony foramen.

The diagnosis was either a tumor or an aneurysm.

Operative Notes (Dr. Grant).—"A left frontal craniotomy was performed. A tumor was seen bulging well laterally to the left of the optic nerve, which had been stretched and thinned by the continuous pressure of the tumor, but which lay well within the lateral confines of the tumor. Gentle palpation of the tumor showed it to be cystic. It was thought that the lesion was probably a craniopharyngioma. In any event, before anything else was done, the cyst was needled and about 10 cc. of pure blood was obtained, with a fairly constant drip through the needle puncture wound. Suddenly, a violent hemorrhage broke from the aneurysm, seemingly central to and below it. It was necessary to amputate the entire left frontal lobe in order to control the bleeding. Clips were put on the left common carotid and the left internal carotid artery. Complete hemostasis was eventually secured, and, after a transfusion of 2 liters of blood, the patient left the table in fairly satisfactory condition. She never regained consciousness, however, and died the following day. Autopsy was not obtained."

The diagnosis was aneurysm of the left internal carotid artery.

Comment.—Although, in a recent paper, Igersheimer concluded that binasal hemianopsia is due to involvement of both optic nerves in front of the chiasm, the situation of the lesion in this case indicates that binasal hemianopsia may be produced by a lesion distinctly lateral to the chiasm. Unfortunately, in neither his case nor in ours was an autopsy obtained. Binasal hemianopsia is certainly suggestive of aneurysm, and such a lesion should be thought of at once in every case with such field defects.

CASE 5.—R. M., aged 50, was admitted to the neurosurgical service on Oct. 10, 1945.

There was a history of failing vision in the left eye for the past year. In February she was in an automobile accident; she ran into a car approaching from the right, which she did not see until it was directly in front of her. Vision was 6/15 and 6/60 on her admission. She was referred by Dr. George Meyer, who had made a diagnosis of intracranial tumor.

The fields showed loss of the upper temporal quadrant on the right side, extending into the lower temporal quadrant, and loss of the entire nasal half of the left field. Since it was known the tumor was a chiasmal one, our analysis indicated a tumor on the left side, impinging on the chiasm from the lateral aspect of its anterior end. Determination of the fields after admission showed a complete right homonymous hemianopsia, with more loss on the left side (fig. 10), indicating that fibers from the upper nasal quadrant of the right eye were now caught and implying that the tumor was progressing backward toward the left optic tract (fig. 11).

Operative Notes (Dr. Grant).—"Just lateral to the left optic nerve was encountered a reddish, fairly well encapsulated tumor, which lay lateral to the left optic nerve. It was obviously lateral to the pituitary fossa. It was finally coagulated, incised and a considerable piece removed with pituitary rongeurs for pathologic verification. It was then the impression that the tumor ran over in the midline and lay in the suprasellar position. The surgeon therefore threw back a right-sided flap in order to expose the right side as well. This was done without difficulty. The dura was much less adherent on this side, and one was able

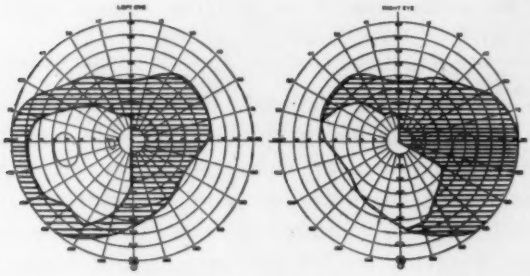

Fig. 10 (case 5).—Peripheral fields showing complete right homonymous hemianopsia, with more loss on the left side. Earlier fields showed a loss of the upper temporal quadrant alone on the right side. That the lower temporal quadrant on the right side is now being caught indicates that the fibers from the upper nasal quadrant of the right eye are being pressed on and implies that the tumor is progressing backward toward the left optic tract.

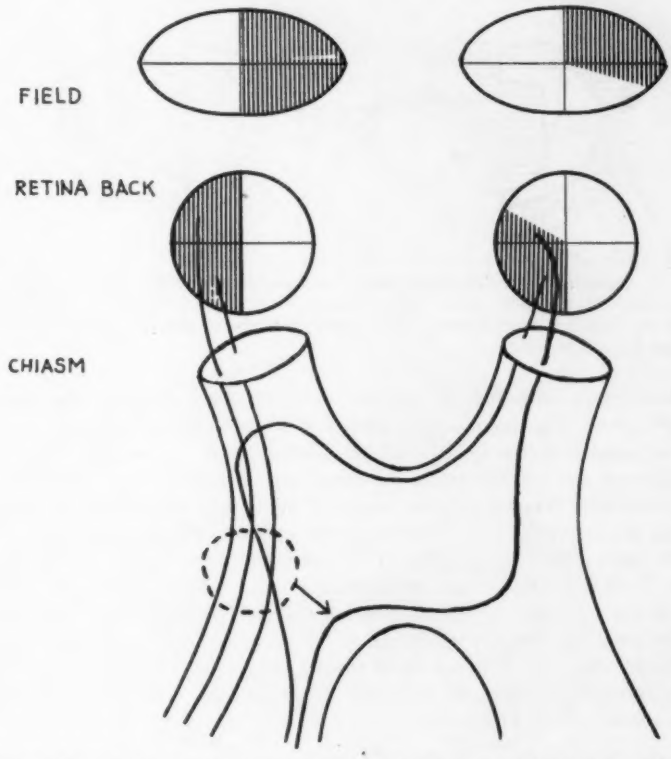

Fig. 11 (case 5).—Probable position of the tumor as indicated by the progression in the loss of the fields.

quite readily to see the right optic nerve, which did not seem to be involved by the tumor. The tumor seemed to lay lateral to, and just behind, the left optic nerve, probably involving the left optic tract."

The diagnosis was chromophobic adenoma of the pituitary gland.

Comment.—In this case, the early field defects, showing only loss of the upper temporal quadrant on the right side, indicated that the lesion was on the left side of the chiasm under the left optic nerve. As the lesion progressed, the lower temporal quadrant on the right side became affected, and this indicated that the tumor was growing backward, probably involving the left optic tract. The diagnosis was verified at operation.

CASE 6.—M. F., aged 16, was admitted to the neurosurgical service on Jan. 20, 1940.

There was a history of decreasing vision in the left eye since August 1939. Fields taken Jan. 5, 1940 at the Lewiston Hospital showed complete right homonymous hemianopsia with loss of central vision in the left eye. The eyes were otherwise normal. The diagnosis was tumor of the left temporal region.

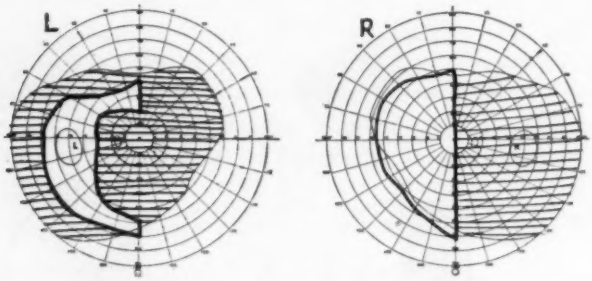

Fig. 12 (case 6).—Peripheral fields, showing loss of the right temporal field and total loss of the left nasal field with extension into the temporal quadrants as far as 30 degrees from fixation and complete loss of the left temporal crescent, leaving an island of vision.

On her admission, the fields (fig. 12) showed total loss of the temporal field in the right eye and a total loss of the nasal field in the left eye. The loss in this field extended over fixation into the temporal field to 30 degrees in the horizontal. There was also complete loss of the temporal crescent, leaving an island of vision. The fields were difficult to analyze. The defect in the center of the left field was too large for a central scotoma. The seeing temporal area was too large for a so-called temporal island. Loss of extreme temporal rim might be interpreted as loss of the temporal crescent belonging to the uniocular field, but there is no place in the chiasm where these fibers alone can be picked out. According to Traquair, the lesion should be back in the left optic tract, with pressure exerted on the tract from the mesial aspect (fig. 13).

Operative Notes.—"Between the left optic nerve and the left internal carotid artery, there presented a calcified artery and a dark green, shiny membrane, which was obviously part of a cyst."

The diagnosis was adamantinoma.

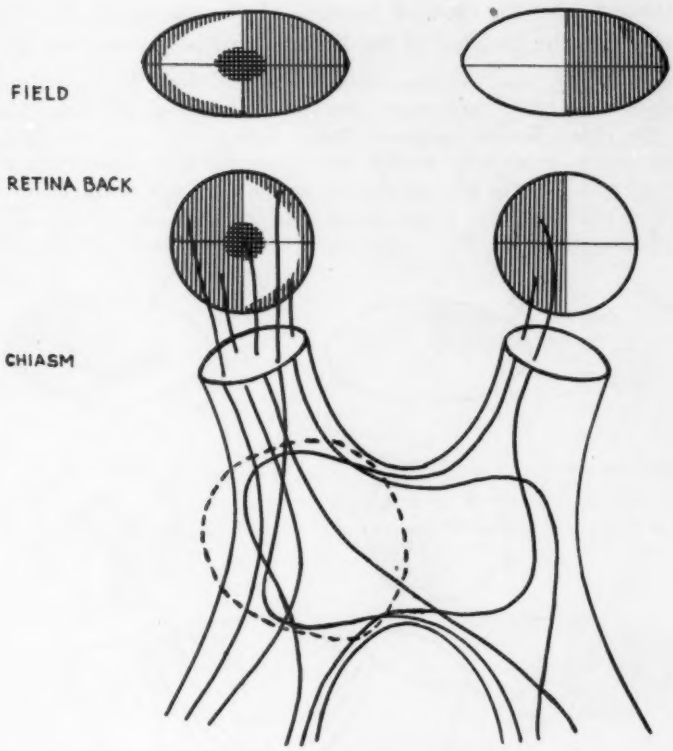

Fig. 13 (case 6).—According to Traquair, the lesion should be back in the left optic tract with pressure exerted on the tract from the mesial aspect.

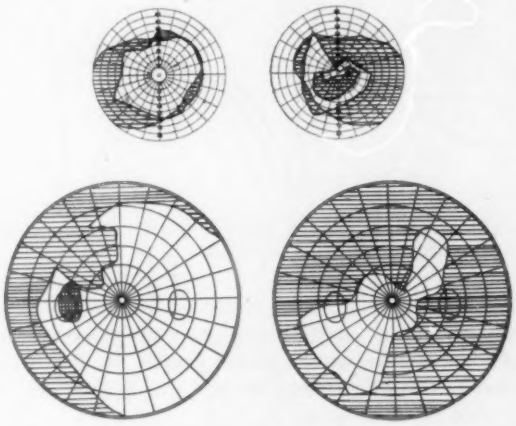

Fig. 14 (case 7).—Peripheral and central fields, showing partial loss of upper and lower temporal quadrants on the right side, with a nerve fiber bundle defect running from the blindspot below fixation to end on the horizontal raphe on the nasal side, and beginning loss of the temporal field in the left eye, more marked in the upper quadrant.

Comment.—In this case, an analysis of the changes in the fields did not agree with the position of the lesion as actually found at operation.

CASE 7.—T. M., aged 46, complained of loss of vision in the right eye and was referred to us by an optometrist, who suspected a chiasmal lesion. The visual field in the right eye was complex. There were partial loss of both temporal quadrants and a nerve fiber bundle defect running from the blindspot below fixation and ending on the horizontal raphe on the nasal half of the field. The left eye showed beginning loss of the upper temporal field and some loss of the lower temporal field (fig. 14). Analysis of the field placed the lesion in the

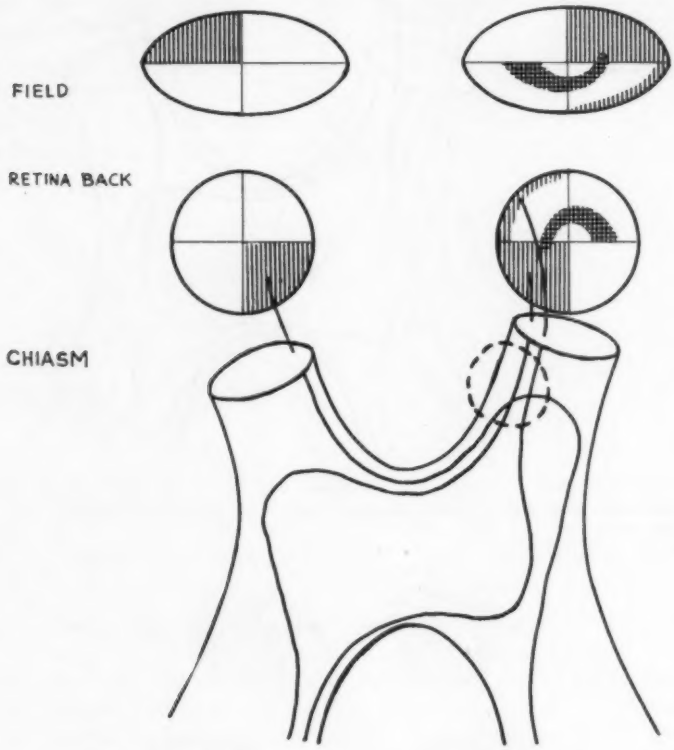

Fig. 15 (case 7).—Analysis of the fields indicating a tumor under the chiasm on the right side, involving the right uptic nerve as well.

right optic nerve, well forward, and probably involving blood vessels of the nerve itself, with production of the nerve fiber bundle defect (fig. 15). Such scotomas are not uncommon with vascular lesions in the nerve. Vision was limited to hand movements in the right eye and was 6/12 in the left eye. Neither eye showed any optic nerve atrophy.

Operative Notes.—"The right optic nerve was humped over a tumor, the spur of which had almost penetrated the center of the nerve. There was a bluish tumor in the fossa. The tumor was needled and no fluid was obtained."

The diagnosis was cystic chromophobic adenoma.

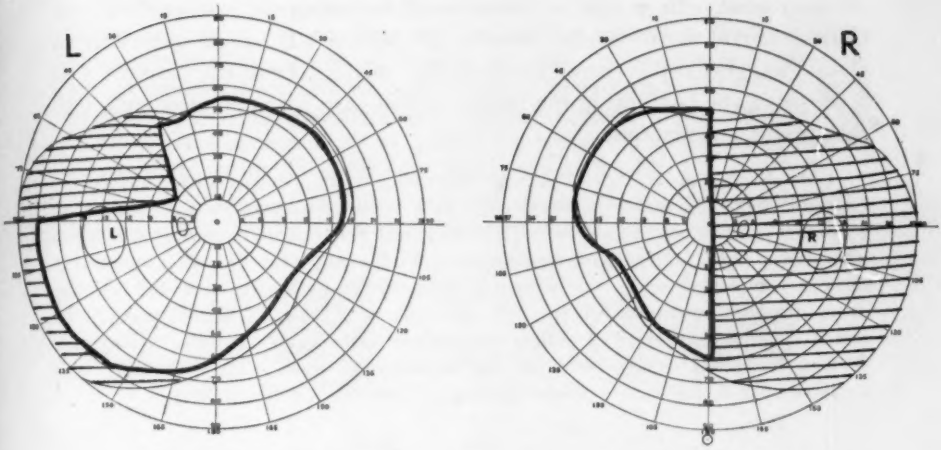

Fig. 16 (case 8).—Peripheral fields to 1/330 white, made on Nov. 25, 1946, showing complete loss of the temporal quadrants in the right eye and loss of the upper temporal quadrant in the left eye. Vision was 20/20 in the left eye and 20/70 in the right eye.

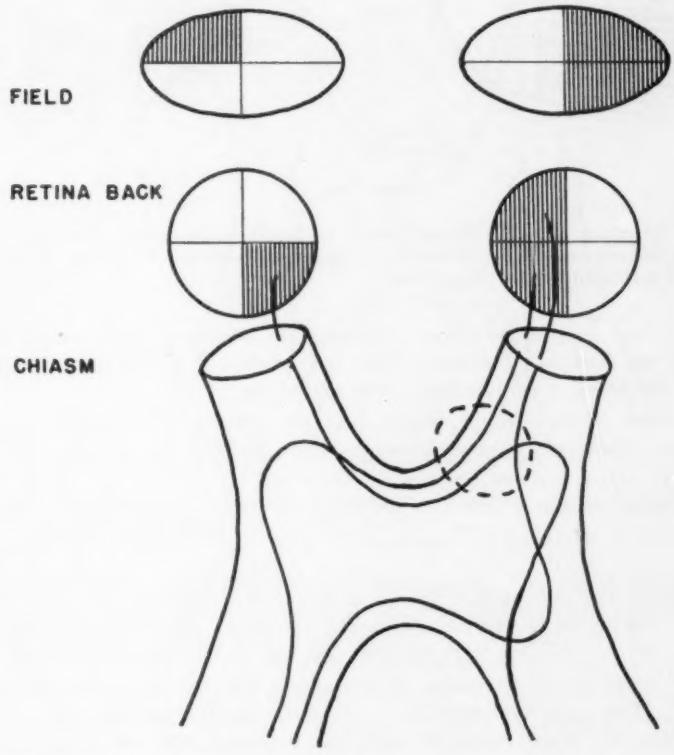

Fig. 17 (case 8).—Analysis of fields indicating a tumor under the anterior end of the chiasm.

Comment.—In a case of bitemporal hemianopsia, cecocentral scotomas, nerve fiber bundle defects or horizontal hemianopic defects should suggest involvement of the nerve on the side of the defect. The analysis of the position of the tumor in this case corresponded well with that found at operation.

CASE 8.—A. di S., aged 32, was admitted to the neurosurgical service on Nov. 24, 1946. Five months previously, at a routine examination for change of glasses, it was found that he had a right temporal field cut. The patient's brother, who was a physician, advised investigation. Fields taken the day after admission showed complete loss of the temporal field of the right eye and loss of the upper temporal quadrant of the left eye (fig. 16). Visual acuity was 20/70 and 20/20, respectively. The patient had definite acromegaly, and roentgenograms showed enormous enlargement of the hypophysial fossa. The diagnosis was an intrasellar lesion with a slight parasellar extension on the right side.

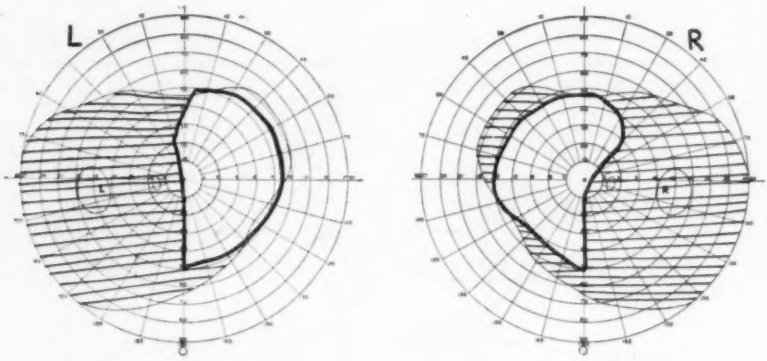

Fig. 18 (case 9).—Peripheral fields to 1/330 white, made on Dec. 7, 1945, showing almost complete bitemporal hemianopsia with some sparing of the upper temporal quadrant on the right side.

The visual fields taken prior to the patient's admission were similar to those taken in the hospital. Analysis of the fields indicated a tumor at the anterior end of the chiasm under the right optic nerve (fig. 17).

Operative Notes.—"Right frontal flap was formed. The right optic nerve was found moderately distended over a bluish, purplish tumor which lay in the sella."

The diagnosis was adenoma of the pituitary gland, predominantly eosinophilic.

CASE 9.—T. H., aged 37, was admitted to the neurosurgical service on Dec. 7, 1945.

History.—The patient had blurred vision in the right eye for three months. She was not helped by change of glasses. Six weeks previously she had noticed that she was not able to see in the temporal half of the right visual field.

Fields made on her admission showed almost complete bitemporal hemianopsia (fig. 18). The upper temporal quadrant of the right field, however, was more spared than the lower temporal quadrant, indicating that the fibers from the lower nasal portion of the retina on the right side were not so much involved

as the fibers from the upper nasal portion of the retina. The fibers from the lower nasal part of the retina are the ones which cross over in the front of the chiasm into the left optic nerve, forming the knee. It would appear, therefore, that the tumor was probably somewhat posterior and a little to the right side, but the fields have little localizing value. Since her vision in the right eye was limited to counting fingers and to 6/22 in the left eye, it was probable that the macular fibers on the right side were also involved (fig. 19).

Operative Notes.—"From the standpoint of physiology and visual fields the diagnosis was a definite lesion of the pituitary gland. The roentgenogram, how-

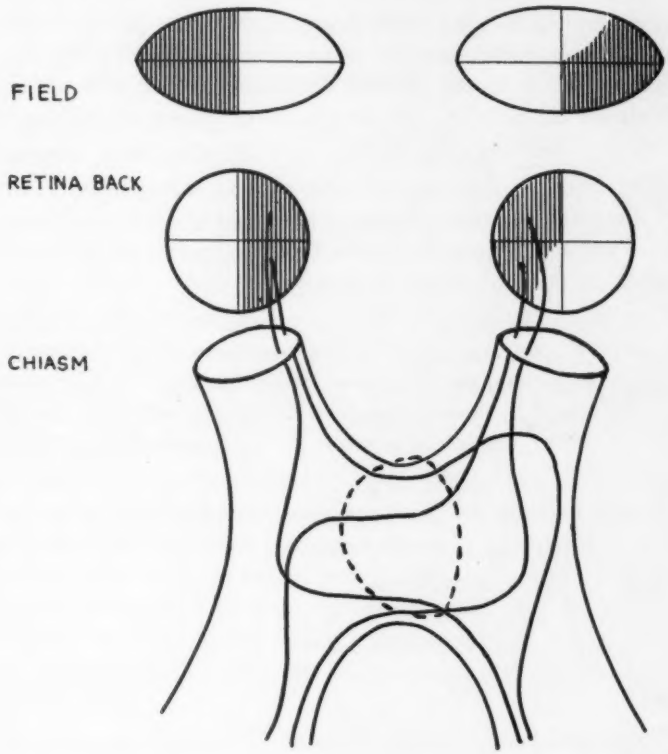

Fig. 19 (case 9).—Analysis of the fields indicating that the fibers from the lower nasal retina on the right side were not so much involved as the fibers from the upper nasal retina. This would indicate that the tumor was somewhat posterior and a little at the right side of the midline.

ever, showed little or no change in the pituitary fossa. The visual acuity on the right side was poorer than on the left, so that the operative approach was from the right side. The orbital plate was exposed and the dura incised along the sphenoidal ridge. This exposed the right optic nerve and the optic chiasm, which was obviously humped upward and forward over a neoplasm. The neoplasm, however, lay more posterior than usual, and its anterior surface could just be glimpsed between the optic nerves. There was a definite furrow in the right optic tract caused by pressure of the right anterior cerebral vessel."

SUMMARY

Nine cases are reported of lesions in the neighborhood of the chiasm which indicate that some information as to the position of the lesion in respect to the chiasm may be gained by an analysis of the early field changes. The visual fields in these cases were such as to suggest the location of chiasmal interference, and after this had been predicated, a comparison was made with the findings at operation. It should be noted that in all these cases it was known that the lesion was in the neighborhood of the chiasm and that only those cases were selected in which the changes in the fields gave some suggestion of the site of interference. Even with these advantages, the localization in several cases was somewhat inaccurate. It would appear, therefore, that in selected cases the early fields are of definite, but not absolute, value in localizing the site of the lesion. The following changes have the greatest localizing value:

1. Bitemporal hemianopic scotoma with or without bitemporal contraction suggests a lesion encroaching on the posterior surface of the chiasm. Typical bitemporal defects may not appear until later. These fields are suggestive of craniopharyngiomas.

2. Loss of one temporal field with loss of the opposite superior temporal quadrant suggests a tumor lying on the side of the greater field loss at the anterior end of the chiasm under the optic nerve. When this picture is followed by loss of the lower temporal field on the side with the quadrant defect, the lesion is probably coming up through the chiasm. These fields seem to be characteristic of adenomas of the pituitary gland.

3. Binasal hemianopsia with one side more complete than the other, especially if extending into the temporal field on that side, indicates pressure at the lateral aspects of the chiasm on both sides. The lesion probably lies on the side with the greater field loss, and the opposite field defect is due to pressure of the opposite internal carotid artery or to pressure of the lateral aspect of the nerve against the bony optic foramen.

4. Bitemporal hemianopic fields with bizarre scotomas, cecocentral, altitudinal or in the nature of nerve fiber bundle defects, indicate a tumor at the anterior end of the chiasm, probably involving the nerve on the side of the scotoma.

Hospital of University of Pennsylvania.

THE CORNEA

I. Swelling Properties of the Fibrous Tunic of the Eye

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THE CORNEA is the most important refractive surface in the eyes of animals living in air. This often overlooked fact places the cornea second only to the retina in importance of the ocular tissues to visual function, for without this effect of the cornea no proper retinal image could be formed. In order for light to reach the retina, it is vital of course that the cornea remain transparent. Opacities of the cornea present a real problem in practical therapeutics and have led, therefore, to a consideration of why the cornea is transparent in the first place, what if anything can be done about opacities of the cornea and why the sclera is not transparent, since it is structurally homologous to the cornea.

In outlining an experimental approach to these questions, we have a number of well known observations to guide us. In the first place, it was pointed out by Walls[1] that cornea and sclera are both transparent in early embryonic development and that in many of the lower animals the sclera of the adult eye is almost as transparent as the cornea. Since the entire fibrous tunic is transparent from the start, perhaps one should ask why the sclera is opaque rather than why the cornea is transparent.

The next observation of importance lies in the histology of the fibrous tunic. The sclera is composed of long collagenous fibers of unknown length felted together very closely. In the cornea, the lamellas are compact but much less felted than in the sclera, and the fibers are parallel and in definite layers. It is well known that pressure on the intact eye produces clouding of the cornea, which disappears again on release of the pressure. Insertion of a needle into the cornea

Supported in part by a grant from the John and Mary R. Markle Foundation.

From the Departments of Ophthalmology and Biochemistry, Temple University School of Medicine.

1. Walls, G.: The Vertebrate Eye and Its Adaptive Radiation, Bloomfield Hills, Mich., Cranbrook Institute of Science, 1942.

leaves an opaque spot, which persists for a prolonged period. These simple and well known observations lead one to expect to find mechanical, as well as chemical, factors in the transmission of light by the fibrous tunic of the eye.

In consideration of the purely chemical factors in this problem, one is reminded that the fibrous tunic is composed of collagenous fibers which on boiling yield gelatin. Extensive chemical studies have been made in years past on tissues of this type, especially on the derived product, gelatin.[2] Therefore, there is much to guide one in previous work, and comparisons should be helpful. It should be pointed out, however, that transmission of light is the dominant consideration in the study of the eye, whereas with other protein systems interest in optical properties has been a minor issue.

The most characteristic feature of the fibrous tunic, in vitro, is that it tends to imbibe fluid in aqueous solutions. Cogan and Kinsey[3] emphasized the water content of the cornea as the chief determining factor in transparency of this tissue, and as the one responsible for the optical difference between cornea and sclera. The first paper of our series, therefore, constitutes a study of the swelling properties of the fibrous tunic. In this paper we show that, although the cornea and the sclera are both composed of collagenous fibers, there is a decided structural difference between the two tissues, as brought out by the striking differences in swelling behavior. These differences in swelling were predicted from what is known of the arrangement of the collagenous fibers from histologic studies, as previously noted. The importance of this structural difference becomes apparent in the second paper, in which we study the factors affecting the transmission of visible light by the cornea and sclera.

METHODS AND MATERIAL

Whole eyes were removed from freshly killed cattle and transported to the laboratory in tap water. The cornea was removed by making a primary incision with a cataract knife and cutting around the corneoscleral junction with iris scissors so as not to include the scleral spur. The epithelium was peeled off early in each experiment.

All observations on swelling were made in buffered solutions of varying composition and hydrogen ion concentration, and all solutions

2. Schmidt, C. L. A.: Chemistry of the Amino Acids and Proteins, Springfield, Ill., Charles C Thomas, Publisher, 1938.

3. Kinsey, V. E., and Cogan, D. G.: The Cornea: III. Hydration Properties of Excised Corneal Pieces, Arch. Ophth. **28**:272-284 (Aug.) 1942; IV. Hydration Properties of the Whole Cornea, ibid. **28**:449-463 (Sept.) 1942; V. Physiologic Aspects, ibid. **28**:661-669 (Oct.) 1942; Physiologic Studies on the Cornea, Science **95**:607-608, 1942.

were adjusted to the same osmotic activity. Although we found, as did Cogan and Kinsey, that adjustment to isosmotic activity did not greatly alter the general results in this study, we present our methods for preparing such solutions, for the benefit of those who have occasion to make similar observations.

Acetate buffer of 0.2 normal strength was chosen because the osmotic activity of the buffer mixture at p_H 5.6 is 9.00 atmospheres, a figure which lies between the values for the two solutions normally bathing the respective surfaces of the cornea. All other buffers of the acetate series were brought to the same osmotic activity by adding dextrose. Buffers made from other ingredients were likewise brought to 9.00 atmospheres by adding dextrose. All solutions were checked with depressions of the freezing point, and the p_H was determined with the glass electrode at room temperature. A simplified technic of calculation was used, which may be applied to any solution. Suitable constants for simplifying calculation were arrived at in the following manner:

Total osmotic activity is given by the equation

$$OP = \frac{N}{V} RT \phi$$

in which OP is osmotic pressure, in atmospheres, N is the number of moles of solute per liter, V is the volume of solution, R is the gas constant (0.082 liter atmosphere per degree per mole), T is the absolute temperature and ϕ is the osmotic coefficient.

Sodium acetate:

1 cc. 0.2 normal (N) sodium acetate (NaAc) = 0.0164 Gm.

$$N = \frac{\text{Cc. 0.2 N NaAc / L.} \times 0.0164}{\text{Molecular weight of NaAc}} \times 2 \text{ (for ionization)}$$

$$\text{At 0.2 N: } \frac{\triangle t}{N}^{4} = 3.58 \text{ C.}; \phi = \frac{3.58}{1.86 \times 2} = 0.962$$

$$\int_{NaAc} = 0.962 \times \frac{0.0164}{82} \times 2 \times 0.082 \times 298 = 0.0094^{5} \frac{\text{atmosphere / cc.}}{\text{NaAc / L.}}$$

$$OP_{NaAc} = \int_{NaAc} \times \text{(number cc. 0.2 N NaAc added per liter)}$$

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4. $\triangle t$ equals lowering of freezing point, expressed in degrees Centigrade. $\frac{\triangle t}{N}$ equals lowering of molar freezing point.

5. To justify the use of 2 twice here: 3.58/1.86 would represent the osmotic activity of one molecule of sodium acetate, just as 3.58/ (1.86 × 2) indicates the osmotic activity of one particle (i. e., one ion) of sodium acetate. In other words, 3.58/1.86 is the molecular osmotic coefficient (ϕ), while 3.58/ (1.86 × 2) is the particular, or ionic, coefficient (ϕ). Thus, if the ionic coefficient is used, one must multiply the number of moles (N) of sodium acetate or acetic acid used by 2 in order to take dissociation into account.

Acetic acid:

$$1 \text{ cc. } 0.2 \text{ normal (N) acetic acid (HAc)} = 0.012 \text{ Gm.}$$

$$N = \frac{\text{Cc. } 0.2 \text{ N HAc/ L.} \times 0.012}{\text{Molecular weight of HAc}} \times 2 \text{ for ionization}$$

$$\text{At } 0.2 \text{ N: } \frac{\Delta t}{N} = 1.88 \text{ C.}; \quad \phi = \frac{1.88}{1.86 \times 2} = 0.506$$

$$\int_{HAc} = 0.506 \times \frac{0.012}{60} \times 2 \times 0.082 \times 298 = 0.00495 \text{ atmosphere / cc. HAc/ L.}$$

$$OP_{HAc} = \int_{HAc} \times \text{(number cc. 0.2 N HAc added per liter)}$$

Dextrose:

$$OP = \phi \frac{N}{V} RT; \quad N = \frac{OP \times V}{\phi RT}$$

$$\frac{1}{(1.01)\ (0.082)\ (298)} \times 180 \times \frac{100}{1{,}000} = 0.727 \text{ Gm. of dextrose/ 100 cc. for 1 atmosphere}$$

Grams dextrose desired at p_H X = (desired $OP - OP_{NaAc} - OP_{HAc}$) $\times$ 0.727

Sample calculation:

$$OP_{NaAc_{8.0}} = 0.0094 \times 910 = 8.55 \text{ atmospheres}$$

$$OP_{HAc_{8.0}} = 0.00495 \times 90 = 0.45 \text{ atmosphere}$$

Total $OP_{8.0} = 9.00$ atmospheres

$$OP_{NaAc_{3.8}} = 0.0094 \times 120 = 1.128 \text{ atmospheres}$$

$$OP_{HAc_{3.8}} = 0.00495 \times 880 = 4.36 \text{ atmospheres}$$

Total $OP_{3.8} = 5.49$ atmospheres

Grams dextrose required at p_H 3.8 = $(9.00 - 1.128 - 4.36) \times 0.727 = 2.55$

For phosphate buffer:

$$\int KH_2PO_4 = 0.003$$

$$\int Na_2HPO_4 = 0.0025$$

The use of this simple means of calculation permits preparation of solutions in which the theoretic osmotic activities agree well with experimentally determined values. The extremes of Δt for acetate buffer were 0.715 and 0.691; for phosphate buffer, they were 0.721 and 0.691.

In the studies on swelling, corneas and pieces of sclera were placed in 100 cc. of buffer solution and held at room temperature. Larger quantities of buffer were found unnecessary, as judged by the stability of the p_H throughout the experiments.

Swelling of the cornea is expressed as the ratio of the weight as determined at any given time to the original wet weight. In experiments with sclera, pieces weighing about 500 mg. were cut. Swelling is expressed in the same manner as that for cornea. At selected logarithmic time intervals, the weight ratios are plotted against the p_H. It is a simple matter to reconstruct the rate curves for swelling from the figures if one so desires.

The data were subjected to analysis by the chi square method.[6] Probabilities were read from pearsonian tables. Where chance differences in swelling existed between two values for the p_H, one of them was omitted in the plotting of data. Chance differences were found for values about the isoelectric point for the acetate buffer, and for values above p_H 6.6 for the phosphate buffer. These points demonstrate the great variability of swelling in this range of p_H. Time intervals were tested for significance in the same manner.

RESULTS

Cornea in Acetate Buffer.—The weight ratio for cornea was a function of the p_H, as shown in chart 1 *A* and *B*, and increased with time to some limiting value, depending on the p_H. A definite swelling minimum was established at p_H 4.6 by the sixty-third hour, which may be taken as the apparent isoelectric point of the cornea At this point the cornea showed negative swelling in these experiments. The existence of an isoelectric point in this region was found also by Cogan and Kinsey.

The effect of failure to equilibrate the osmotic activity in the various solutions is shown in chart 1 *B*. On the alkaline side of the isoelectric point, the rate of swelling was greater in the presence of osmotic correction, although the total swelling attained at sixty-three hours was about the same. On the acid side of the isoelectric point, however, swelling was greater in both rate and amount in the absence of osmotic correction.

If the cornea was dried in air to constant weight before being placed in the buffer solutions, it swelled in the same manner as fresh cornea, as shown in chart 2. At p_H 5.6 the rate of swelling after two and a half hours and the maximum of swelling at forty hours were identical with the values for the fresh cornea. However, at p_H 3.6, both rate and swelling maximum were greater for dried cornea.

Cornea in Phosphate Buffer.—The rate of swelling of cornea in phosphate buffer was much less than that in acetate buffer (chart 3), as one would expect from the known effects of valence of acids on imbibition. In the Donnan effect, monobasic acids affect swelling of a protein according to the equation $y\,(y+z)=X^2$, while dibasic acids behave as $y^2\,(y+z)=X^3$. Great variability in swelling was found

6. Yule, G. U.: Theory of Statistics, ed. 10, London, Charles Griffen & Company, Ltd., 1936, p. 370.

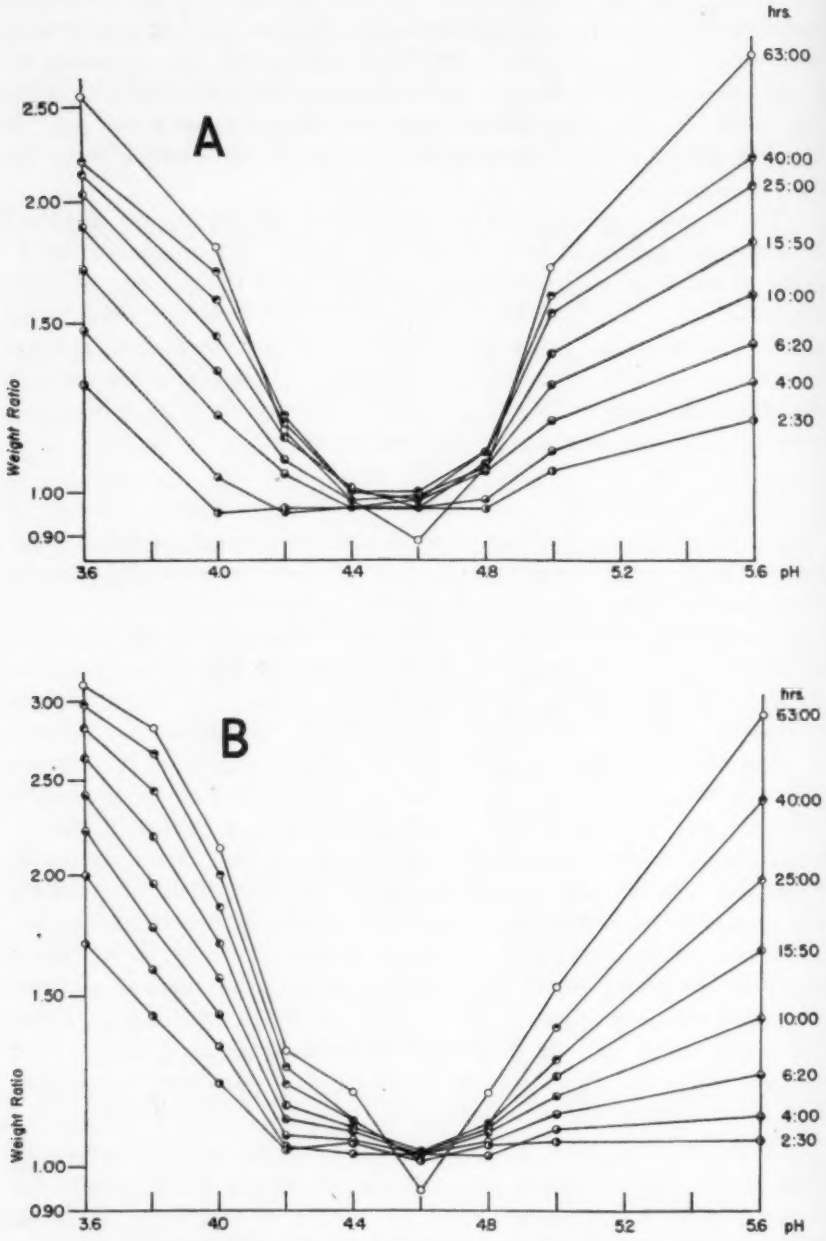

Chart 1.—*A*, swelling of cornea in isosmotic, 0.2 normal acetate buffer solutions. *B*, swelling of cornea in 0.2 normal acetate buffer solutions, without osmotic correction.

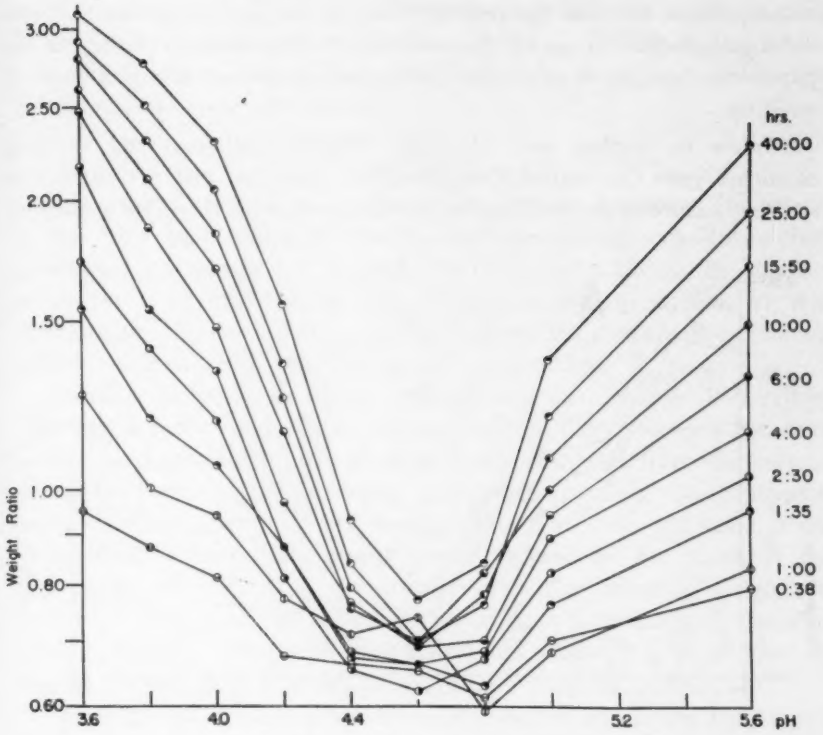

Chart 2.—Swelling of dried cornea in isosmotic, 0.2 normal acetate buffer solutions.

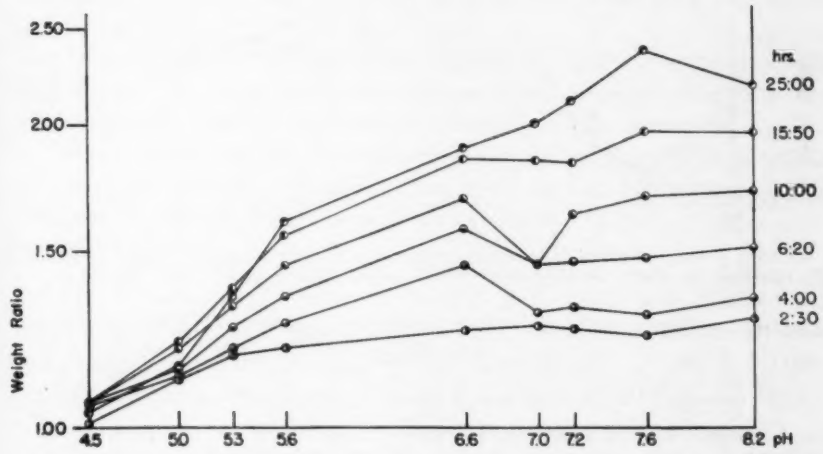

Chart 3.—Swelling of cornea in isosmotic, 0.0667 normal phosphate buffer solutions.

at a p_H above 6.6, and the points shown in the figure represent chance differences. This suggests the advisability of studying swelling in the physiologic range of p_H values with continuous recording of rate of swelling.

Sclera in Acetate and Phosphate Buffer.—Whereas the swelling of cornea gave the beautiful mathematical functions just presented, the striking feature of the swelling of scleral tissue under the same conditions

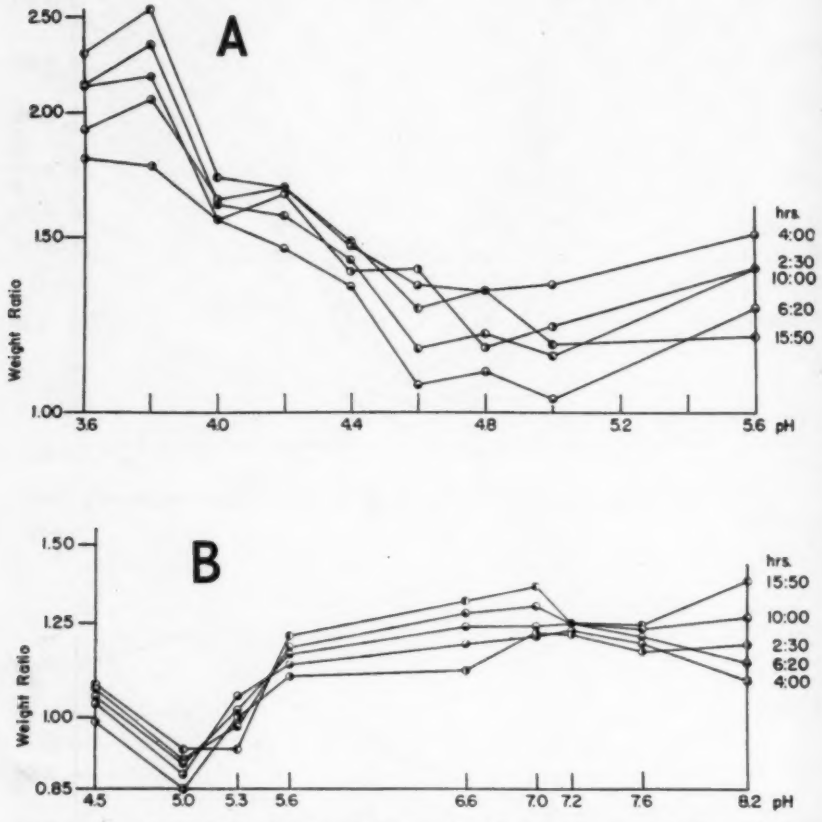

Chart 4.—*A*, swelling of sclera in isosmotic, 0.2 normal acetate buffer solutions. *B*, swelling of sclera in isosmotic, 0.0667 normal phosphate buffer solutions.

was its erratic behavior. This is well brought out by inspection of chart 4 *A* and *B*. The general configuration of chart 4 *A* suggests that scleral tissue tends to swell in a manner comparable to corneal tissue.

Changes in Viscosity in Cornea.—Regardless of the buffer used, corneas at p_H 3.6 were in general observed to be very firm in consistency. This firmness was observed to a lesser degree in all buffers up to p_H 5.0, at which point the cornea was soft. It was very soft at

p_H 5.6 and above. The degree of firmness or softness at the various values for the p_H was subject to some variation, according to the electrolyte added. At p_H values above the physiologic range, corneas became gelatinous and went into solution.

COMMENT

The cornea swells in a regular and predictable manner. The sclera, on the other hand, swells erratically. It is reasonable to postulate that, although both tissues are composed of collagenous fibers, the lamellar arrangement of fibers in the cornea permits orderly swelling of that tissue, while the dense felting of the fibers in the sclera sets up strong cohesive forces which interfere with free swelling.

Another factor is yet to be evaluated in differentiating the swelling behavior of cornea and sclera. Meyer and Chaffee [7] isolated a naturally occurring monosulfuric acid ester of hyaluronic acid from the cornea. The ester forms a stable complex with protein. Since this compound is not found in sclera, one may assume that it accounts for some of the differences between cornea and sclera, as well as for some of the unexpected deviations of the cornea from the behavior of gels in general—for example, the failure of imbibition to correlate with viscosity. This compound remains to be isolated and studied, in order that its role in the swelling behavior of the cornea may be assessed.

Heringa and associates [8] studied the effect of extracting the mucoid on swelling of the cornea in 100 per cent water vapor. Swelling was thereby reduced from thirty to thirteen times the dry weight. Water absorption isotherms for cornea and sclera were found to coincide below an 80 per cent saturation of the atmosphere but diverged widely above this point.

Gelatin gels have been so thoroughly studied that it may be profitable to point out the similarities and differences in behavior of gelatin and the substantia propria (collagenous fibers) of the cornea.

When gelatin swells in saline solutions, the concentration of salt in the swollen particles is practically the same as that in the surrounding medium, as though water went in by capillarity. Holt and associates [9]

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7. Meyer, K., and Chaffee, E.: Mucopolysaccharide Acid of Cornea and Possible Relation to the "Spreading Factor," Proc. Soc. Exper. Biol. & Med. **43**:487-489, 1940; The Mucopolysaccharide Acid of the Cornea and Its Enzymatic Hydrolysis, Am. J. Ophth. **23**:1320-1325, 1940.

8. Heringa, G. C., and Weidinger, A.: Structure and Importance of Connective Tissue: XI. Water Binding in the Intermediary Substance, Nederl. tijdschr. v. geneesk. **84**:4907-4917, 1940. Leyns, W. F.; Heringa, C., and Weidinger, A.: Water Binding Capacity of Cornea, Acta brev. Neerland. **10**:25-26, 1940.

9. Holt, M., and Cogan, D. G.: The Cornea: VIII. Permeability of the Excised Cornea to Ions, as Determined by Measurements of Impedance, Arch. Ophth. **35**:292-298 (March) 1946.

showed that the resistence of corneal stroma to the passage of ions is about that offered by an equivalent volume of isotonic solution of sodium chloride. As for nonpolar substances, Collander [10] found that gelatin membranes show no preferential permeability to lipid substances. Swan and White [11] showed that the corneal stroma permits ready entrance of polar and surface-inactive compounds, while nonpolar and surface-active compounds pass less readily. On the other hand, the presence of the corneal epithelium causes nonpolar compounds to penetrate the stroma more readily and polar compounds less readily. Cogan and co-workers [12] confirmed these findings, emphasizing that purely water-soluble substances do not pass the epithelium and purely fat-soluble substances do not pass the stroma, and pointed out that substances which pass whole cornea have biphasic solubilities, with the exception of water.

The isoelectric point of the substantia propria of the cornea corresponds well with that for pure gelatin. The fact that the cornea may be dried to constant weight and then found to follow a swelling curve similar to that for normal cornea shows the minimum of "hysteresis" effect. The latter term is used to denote the "memory" of colloid systems and indicates the effect of previous history on behavior. This finding is an important practical point in the problem of corneal transplantation and represents an interesting departure from pure gelatin, since Gortner and Hoffman [13] found that drying had a profound effect on rate of rehydration and maximum imbibition of gelatin particles.

It is interesting to note that mechanical distortion of a gelatin block produces an optical birefringence similar to that seen in cornea. In gelatin, however, the anisotrophy disappears slowly on release of pressure, while in the cornea the return to the original state is sudden, no doubt due to elastic components of the substantia propria. This phenomenon probably represents in both instances a rod-structural type of birefringence. Further comment on its causation and its significance in the transparency of the cornea will be made in the second paper.

No one mechanism has been found adequate to explain the swelling of proteins under all conditions. Using the roentgen ray diffraction

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10. Collander, R.: Einige Permeabilitätversuche mit Gelatinemembranen, Protoplasma **3**:213-222, 1928.

11. Swan, K. C., and White, N. G.: Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043-1057, 1942.

12. Cogan, D. G.; Hirsch, E. O., and Kinsey, V. E.: The Cornea: VI. Permeability Characteristics of the Excised Cornea, Arch. Ophth. **31**:408-412 (May) 1944. Cogan, D. G., and Hirsch, E. O.: The Cornea: VII. Permeability to Weak Electrolytes, ibid. **32**:276-282 (Oct.) 1944.

13. Gortner, R. A., and Hoffman, W. F.: The Imbibition of Gelatin Dried as a Gel and as a Sol, J. Phys. Chem. **31**:464-466, 1927.

technic, Katz [14] distinguished intermicellar, intramicellar and permutoid (chemical compound formation) types of swelling. Histologic sections of the cornea stained with Mallory's aniline blue show that the swelling is both between and within the lamellas.

In summary, it may be said that the fibrous tunic of the eye is analogous to gelatin in swelling behavior. The significance of this observation is that the cornea and sclera are both lyophilic colloid systems and are subject to the same general rules of behavior as are such systems in general. Such differences as are noted in swelling behavior between cornea and sclera can be explained as largely due to differences in mechanical arrangement of the fibers. The presence of hyaluronosulfuric acid in cornea and its absence from sclera is another factor yet to be evaluated.

Dr. R. H. Peckham made mathematical examination of the data and constructed the figures.

14. Katz, J. R.: The Laws of Swelling, Tr. Faraday Soc. **29**:279-297, 1933

THE CORNEA

II. Factors Affecting the Transmission of Visible Light by the Fibrous Tunic of the Eye

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THE CLINICAL problem posed by opacification of the cornea stimulated an early interest in the factors responsible for transparency of this tissue and the possible explanations for its striking dissimilarity to the sclera. The most recent attack on this problem has been made by Cogan and Kinsey,[1] who reviewed the pertinent work before their time. These authors emphasized the water content of the cornea as the chief determining factor in the transparency of this tissue and as responsible for the optical difference between cornea and sclera. According to their concept, the cornea is endowed with a dehydrating mechanism (in the form of semipermeable endothelium and epithelium) to keep down its water content. When this mechanism fails, swelling, and therefore opacification, occurs. The sclera, on the other hand, is said to be opaque because of the absence of any such mechanism.

While studying swelling of the cornea, we had ample opportunity to determine the effect of water content and other factors on the optical properties of the cornea. In the present paper we shall show that there is a rough inverse relation between the degree of swelling and the degree of turbidity of the cornea under the conditions of our experiments and, further, that the cornea may remain transparent despite any degree of swelling. The factors responsible for corneal transparency are analyzed, and the theoretic approach to the clinical problem of corneal opacity is given.

This study was supported in part by a grant from the John and Mary R. Markle Foundation.

From the Departments of Ophthalmology and Biochemistry, Temple University School of Medicine.

1. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, Arch. Ophth. **28**:661-669, (Oct.) 1942; Physiologic Studies on the Cornea, Science **95**:607-608, 1942.

METHODS AND MATERIALS

The technics for studying beef corneas reported in the previous paper [2] were used. All buffer solutions were adjusted to the same osmotic activity (9.00 atmospheres) as before. An arbitrary scale was used for evaluating the degree of turbidity of the cornea. A black line on a piece of white paper was viewed through the cornea. Recordings of turbidity were made as 0, 1, 2, 3 and 4, in which 0 indicated normal cornea, 4 a completely opaque cornea and 1, 2 and 3 inter-

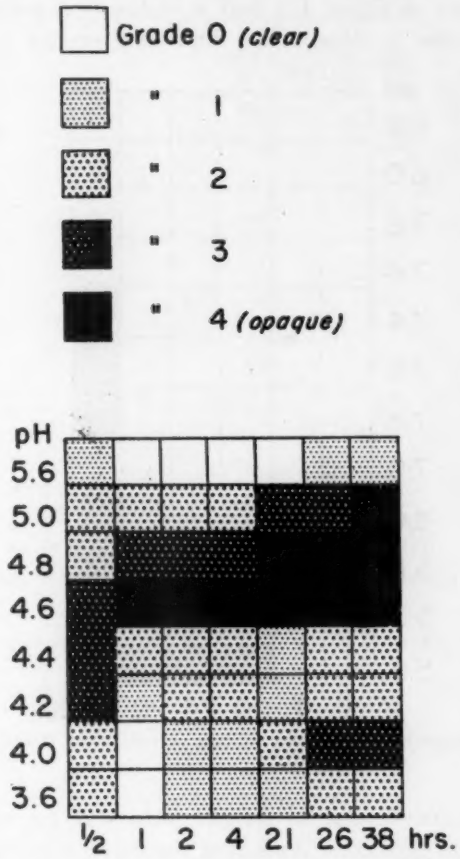

Chart 1.—Changes in turbidity in corneas in isosmotic, 0.2 normal acetate buffer solutions.

mediate stages. Control observations by independent observers quickly established the reliability of these readings. After practice was gained, plus values were used as interpolations in these readings. Obviously, photographic transmission data would represent more accurate nephelometry, but for present purposes the arbitrary scale is in many ways superior.

2. Hart, W. M., and Chandler, B. F.: The Cornea: I. Swelling Properties of the Fibrous Tunic of the Eye, Arch. Ophth. **40**:601 (Dec.) 1948.

In constructing charts 1, 2, 3 and 4, the five arbitrary steps of optical difference were represented by areas of stippling and solid black. All turbidity readings were reported after removal of the epithelium. In determining the effects of electrolytes on turbidity, each solution was made 0.01 normal with respect to the electrolyte in question.

RESULTS

Degree of Swelling.—The weight ratio for cornea is a function of the p_H, as shown in figure 1 *A* and *B* of the first paper, and increases with time to some limiting value, depending on the p_H.[3] If turbidity

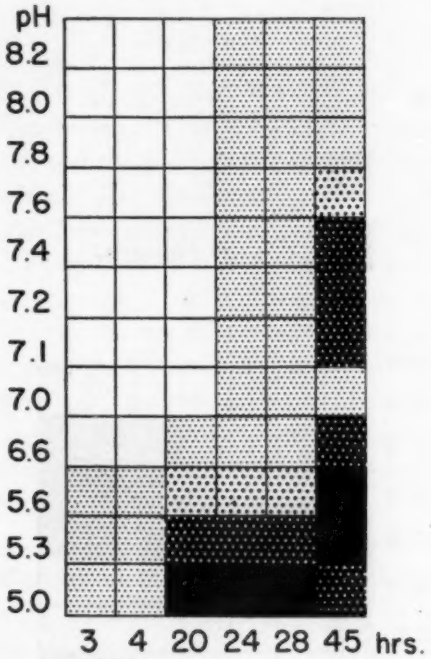

Chart 2.—Changes in turbidity in corneas in isosmotic, 0.0667 normal phosphate buffer solutions.

is plotted with coordinates of weight ratio and p_H, weight ratio and time, and p_H and time, one finds that turbidity is independent of time and the weight ratio. Although weight ratio and turbidity are both functions of the p_H, they relate to the p_H in an inverse manner, as shown in chart 5. In addition to the influence of the p_H, turbidity is affected by the presence of certain electrolytes, as noted later. In acetate buffer, the turbidity is grade 4 at the isoelectric point (p_H 4.6), where the cornea actually loses in weight, while at p_H 5.6 and p_H 3.6, where swelling is great, the transmission of light is excellent.

3. The extent of swelling to be expected at each p_H value for any particular buffer may be found by consulting our previous paper.

If the cornea is placed in 0.001 normal hydrochloric acid, as shown in table 1, the swelling ratio is 2.0 at forty-eight hours, and grade 4 turbidity is reached by the twentieth hour. When the cornea is placed in 0.01 normal hydrochloric acid, the weight ratio is 4.5 at forty-eight hours, while the turbidity remains at grade 0 throughout the period.

TABLE 1.—*Swelling and Turbidity of Corneas in Isosmotic Solutions of Hydrochloric Acid at p_H 2 and p_H 3*

	p_H 2 0.01 Normal Hydrochloric Acid Solution		p_H 3 0.001 Normal Hydrochloric Acid	
Time, Hr.	Weight, Mg.	Turbidity	Weight, Mg.	Turbidity
0	870	0	405	0
1	...	0	690	0
2	950	0	810	0+
3	1,160	0+	875	1
5	1,300	0+	955	3
7	...	..	950	3+
19	1,590	0+	910	4
22	1,615	0+	915	4
24	1,640	0	960	4
27	1,655	0	905	4
30	1,650	0	870	4
44	1,700	0	800	4
48	1,680	0	850	4

Effect of Previous Drying.—Cornea which has first been dried in air shows improved transmission of light in acetate buffer and is at least as good as fresh cornea in phosphate buffer. In chart 3, for example, the turbidity is only grade 1 after seven hours at the isoelectric point, while it is grade 4 for fresh cornea. The findings for phosphate buffer are shown in chart 4. The improved transmission of light of previously dried cornea, which is especially evident at the isoelectric point, suggests the operation of some factor, as yet unknown, other than the p_H.

TABLE 2.—*Changes in Turbidity in Air-Dried and Ether-Extracted Corneas in Acetate Buffer Solutions*

	p_H						
Time, Hr.	3.6	4.0	4.4	4.6	4.8	5.0	5.6
0	0	0	0	0	0	0	0
¼*	1	1	1	1	0+	0+	1
2	1	0	0	0	0	0	0+
4	2+	1+	1+	1	1	2	1+
20	2	3	3	2	1	3	2
25	3	3+	3	2	1+	3	2+
49	3+	3+	3	3	..	4	3

* The reading at the end of one-fourth hour was taken in the presence of epithelium.

In order to determine whether the improvement in turbidity was related to the fat content of the cornea, dried corneas were subjected to continuous extraction with ether for twenty-four hours before the swelling experiments were begun. As shown in table 2, the result is not significantly different from that for dried, nonextracted cornea.

Temperature.—When the temperature was lowered to 10 C., as shown in table 3, no noticeable change was produced except for a tendency of the maximum turbidity to shift from a p_H of 4.6 to a p_H 4.8. Increase in the temperature to 40 C. produced obvious improvement in

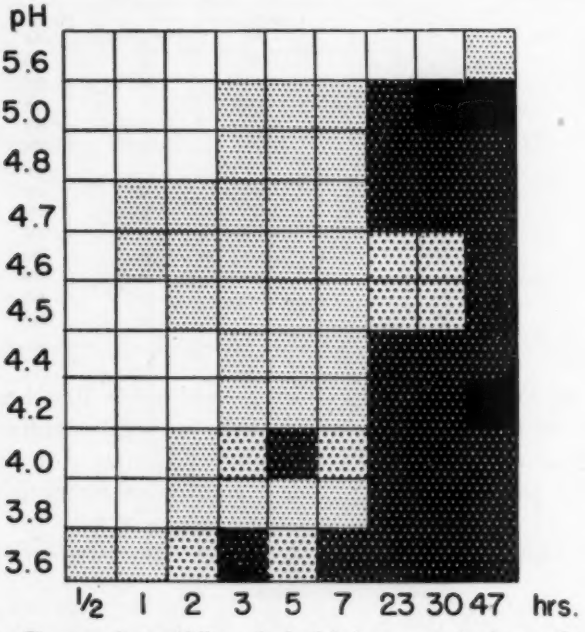

Chart 3.—Changes in turbidity of air-dried corneas in isosmotic, 0.2 normal acetate buffer solutions.

optical effect, especially about the isoelectric point, as shown in table 4. The degree of swelling at these temperatures was of the same order as that at 25 C. (including negative swelling at the isoelectric point).

Electrolytes.—The left column of table 5 shows turbidity readings on the cornea in acetate buffer at p_H 4.6 with no additional salts. Some ions, e. g., $Na+$, $Fe++$, $Ca++$, $SCN-$ and PO_4--- lessen turbidity at this p_H. At p_H 3.6, all added ions produced some increase in turbidity, as seen in table 6. Table 7 shows considerable variation at p_H 5.6. The PO_4--- ion caused no change in turbidity. $Cu+$ and $Ba++$, in particular, caused a notable increase in turbidity. All other ions increased turbidity to some extent.

Opacity of the Cornea.—Opacities of the cornea are comon in cattle. Eyes were brought to the laboratory with dense white opacities; many had deep ulcer craters and profuse fibroblastic invasion. Clearing of such corneas may be produced in one of two ways: (1) by simply

TABLE 3.—*Changes in Turbidity of Corneas in Acetate Buffer with Added Dextrose, at 10 C.*

	p_H							
Time, Hr.	3.6	4.0	4.2	4.4	4.6	4.8	5.0	5.6
0	0	0	0	0	0	0	0	0
½*	2+	1+	1	1	1	0+	0	0
¾	2	4	3+	3	1+	2	0+	0
1	0	2+	3+	2+	2	2	0	0
2	1	1+	4	2+	3	4	1+	0+
3	0+	1	2+	3+	3	3+	1+	0
4	1	1+	2	3+	3	4	1+	0
8	1+	2	2+	4	4	4	2	0
22	1+	2	3	4	3	4	2+	0
26	1+	2	3	3+	3+	4	2+	0
50	1+	2	3	4	3+	4	3	0
75	2	3	3	4	3+	4	3	0
100	2	3	3	4	3	4	3	1+

* The first reading, at one-half hour, was taken in the presence of epithelium.

TABLE 4.—*Changes in Turbidity of Corneas in Acetate Buffer with Added Dextrose, at 40 C.*

	p_H							
Time, Hr.	3.6	4.0	4.2	4.4	4.6	4.8	5.0	5.6
0	0	0	0	0	0	0	0	0
½	1	1	1+	1+	1+	1+	0	0
¾	1	1	1+	1+	1+	1+	0+	0
1	1	1	1+	1+	1+	1+	0+	0+
2	1+	1+	2	1+	1+	2	1+	0+
3	1+	1+	1+	1+	1+	1+	1+	1
4	1+	1+	1+	1+	1+	1+	1+	1
8	2+	3+	2+	2	2	1+	1	0+
22	2+	2+	2+	2	2	2	1+	1+
26	3	3	3	1+	1+	1+	2	0+
50	3+	3+	2+	1+	1+	2	2+	1+
75	4	4	3	1+	1+	1+	2	2
100	4	4	3	1+	1+	1+	1+	2

drying in air, or (2) by swelling in 0.01 normal hydrochloric acid, phosphate or acetate buffer at proper hydrogen ion concentration. When the dried corneas are rehydrated in these solutions they follow normal swelling curves and remain clear.

COMMENT AND CONCLUSIONS

Throughout these observations a rough inverse relation with respect to the p_H existed between the degree of swelling and the turbidity of the

cornea. In addition to the influence of the p_H, turbidity was specifically affected by certain ions, as already noted.

M. Fischer [4] concluded that simple absorption of water does not lead to corneal opacity. He studied the effects of ions on swelling and

TABLE 5.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at p_H 4.6*

Time, Hr.	Buffer Alone	Ca^{++}	K^+	Ba^{++}	Cu^+	Li^+	Mg^{++}	Fe^{++}	Na^+	SCN^-	Citrate	SO_4^-	PO_4^{---}
¼	3*	2	2	2+	3	2	2	2	2+	..	2+	..	..
½	4	..	..	..	..	..	..	..	..	3	2+	2+	1
1	4	2+*	3+*	3+	3+*	3+*	3+*	3+*	3*	3*	3+*	3*	1
2	4	3	4	4	4	4	3+	3+	3	3	3+	4	3+
3	4	3	4	4	4	4	3+	3+	3	3+	4	3+	3+
4	4	3+	4	4	4	4	4	3+	3	3+	4	3+	3+
20	4	3	4	4	4	4	4	3+	3	3+	4	4	4

* Epithelium removed; epithelium remained on in the solution containing barium.

TABLE 6.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at p_H 3.6*

Time, Hr.	Buffer Alone	Ca^{++}	K^+	Ba^{++}	Cu^+	Li^+	Mg^{++}	Fe^{++}	Na^+	SCN^-	Citrate	SO_4^-	PO_4^{---}
¼	..	3+	3	3+	3+	3	4*	3+*	3+*	..	..	..	..
½	2+	..	..	..	..	..	2	..	..	2+*	2+*	2+*	0*
1	0+*	1*	0+*	1*	1+*	1+*	2+	1	1+	2	1+	2	1+
2	1+	2	1	1+	2	1	2	1+	2	1+	2	2	1
3	1+	2	1+	2	2	2	2	2	2	2	1+	2	1
4	..	1+	2	2	2+	2+	2+	1+	2	2	2	2	1
20	1	2+	2+	3	2+	2	2	2	2	2	2	3	1+

* Epithelium removed.

TABLE 7.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at p_H 5.6*

Time, Hr.	Buffer Alone	Ca^{++}	K^+	Ba^{++}	Cu^+	Li^+	Mg^{++}	Fe^{++}	Na^+	SCN^-	Citrate	SO_4^-	PO_4^{---}
¼	..	0	0—	0—	0—	0—	0	1	0	..	..	..	..
½	1	..	..	..	..	..	..	2—	..	0—	1	0—	0
1	0—*	1	1—	2—	3—	2	2	3	2	2	1	2	0—
2	0—	2—	1*	3	3—	3	2	2—	2	2	2	2	0—
3	0—	2—	1	3	4	2—	2	2—	2	1—	2	2	0—
4	0—	2	1	3—	4	3	2	2	2	2	2	2	0—
20	0—	1*	1—	2*	4	2*	1*	2	3	2—	1*	2—	1—
46	1	1	0—	2	4	1	1	2	3	2—	1	0—*	1—

* Epithelium removed; epithelium remained in solutions containing Cu^+, Fe^{++}, Na^+, PO_4^{---} and SCN^-.

the transmission of light by the cornea in 1/110 normal solutions of hydrochloric acid. Besides noting a discrepancy in the amount of water imbibed and the degree of turbidity of the cornea, he found that

4. Fischer, M.: Oedema, New York, John Wiley and Sons, Inc., 1910, p. 136.

citrate, acetate and sulfate ions inhibited corneal opacity in the acid solutions, while thiocyanate, nitrate, bromide and chloride ions favored corneal opacity. Fischer found also that subconjunctival injection of 5 to 15 drops of "hypotonic" or "hypertonic" solutions of sodium citrate (one-eighth to one-sixth molar) lowered the tension in glaucomatous eyes and caused improvement in the steamy cornea. Although we have not attempted such clinical observations, we have not found that citrate influences cornea favorably in the presence of the acetate ion.

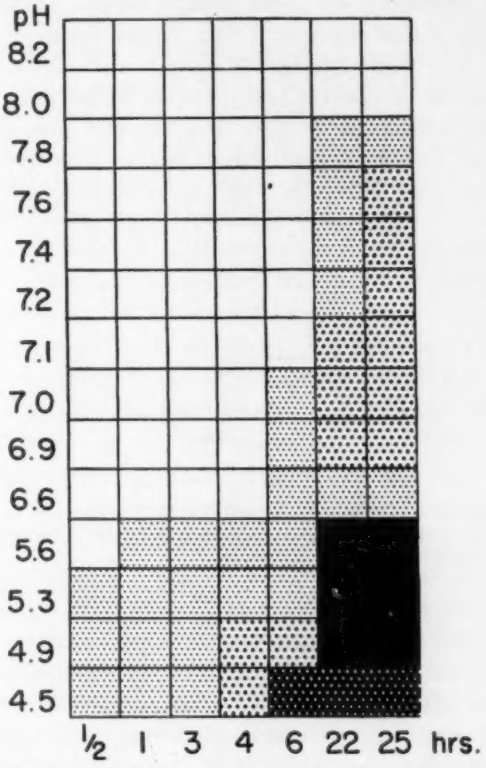

Chart 4.—Changes in turbidity of air-dried corneas in isosmotic 0.0667 normal phosphate buffer solutions.

F. P. Fischer [5] found that reducing the water content of the sclera below 40 per cent or increasing it above 80 per cent rendered this tissue transparent. Although we have not attempted to verify these limits, we have found Fischer's observation correct provided one controls the hydrogen ion concentration and ionic composition of the medium in which the sclera swells.

5. Fischer, F. P.: Experimentelle Untersuchungen an der Lederhant, Arch. f. Augenh. **97**:467, 1926, cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1946, vol. 1, p. 477.

It is well known that swelling of the cornea resulting from damage to its membranes (as in glaucoma) causes clouding. We believe that this effect is determined by the "state" of the water which enters the cornea. Biomicroscopy and fixed histologic sections show that in such conditions water enters the cornea as fine droplets, which remain discrete and progress through the thickness of the substantia propria. This effect, too well known to be described here, is spoken of as a "bedewing" or "steaminess," terms which are descriptively accurate in view of the dispersion of light which results. The semipermeable features of the endothelium and epithelium (with respect to sodium chloride), so well demonstrated by Cogan and Kinsey, may thus subserve the interests of corneal transparency by keeping down the water content of the substantia propria and thereby preventing this effect, although an increase in water content per se does not produce opacification. The possible effects of changes in hydrogen ion concentration

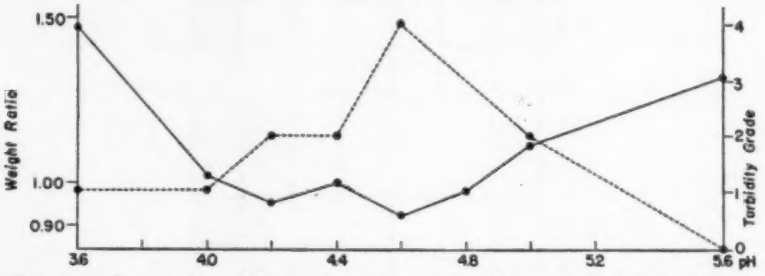

Chart 5.—Curves for weight ratio and turbidity of cornea in 0.2 normal acetate buffer solution at end of four hours, showing a roughly inverse relation between swelling and turbidity as related to the p_H.

and alterations in electrolyte content in such circumstances are thus far unknown but may be presumed to play a part.

In view of the inverse relation between swelling and turbidity of the cornea, the effects of electrolytes, temperature, hydrogen ion concentration and other factors, and the fact that the sclera becomes transparent when properly hydrated, it is obvious that one must look for explanations other than the degree of turgescence or deturgescence to account for the optical difference between cornea and sclera. In so doing, one may list at least three possibilities: (1) differences in refractive index between solvent water and micelles; (2) birefringence phenomena resulting from the fibrillar structure of the fibrous tunic, and (3) the state or dispersion of water in the cornea and sclera, as previously noted.

It is obvious that if the refractive index of the solvent water in the cornea becomes very different from that of the particles, turbidity results. The first step, then, is to list the factors which may affect the refractive index of each. Affecting the micellar refractive index are

(1) temperature, (2) electrolytes, (3) isoelectric point, (4) hydrogen ion concentration, (5) dissociation, (6) mechanical stresses (as in birefringence), (7) hysteresis and (8) coacervate formation (due to protein-lipid-carbohydrate complexes).

Affecting the refractive index of the solvent water are (1) temperature, (2) electrolytes, (3) hydrogen ion concentration, (4) nonelectrolytes and (5) surface tension. The operation of most of these factors is readily apparent in the data presented in this paper and requires no further comment. No doubt there are others which we have not listed.

In consideration of the birefringence phenomenon, we have the well known observation that pressure on the intact eye produces clouding of the cornea. When this pressure is released, the cornea suddenly returns to its original clear state. Cogan and Kinsey [1] accepted the theory of Verrijp that pressure on the eye forces fluid from the structural components into the interstices. The difference in the refractive indexes of the two fluids, according to this theory, becomes apparent as a clouding. It should be pointed out, however, that such pressure is distributed equally in all directions and therefore should tend to force as much fluid in as is forced out of the structural components. We believe this phenomenon may be a true birefringence with the optical axis perpendicular to the corneal curvature at all points. When pressure is applied to the eye, this axis is rotated into the plane of the cornea, and interference with transmission of light results. Such a hypothesis has the merit at least of being amenable to experimental test and will be the subject of our further investigation.

In proposing a theory to account for all the phenomena observed thus far, the cornea may be said to be transparent for two reasons: (1) The spatial arrangement of its fibers has permitted a balance of intramicellar and extramicellar fluid, such as would keep the refractive indexes in the two situations equivalent, and/or (2) the spatial arrangement and organizational plan of fibers have permitted the orderly birefringent mechanism already referred to. It will be recalled that passage of a needle into the living cornea produces a persistent opacity at the site. This opacity is probably due to mechanical disarrangement of the fibers, which produces a local effect similar to that seen when the whole eye is pressed. The distortion of fiber pattern produced by fibroblastic retraction produces a similar effect in a healed corneal lesion. The use of ethyl morphine hydrochloride U. S. P. in treatment of corneal opacity, although of doubtful efficiency, has a good foundation in that its irritating properties cause it to act as a lymphagogue, with a tendency to mechanical redispersion of the corneal fibers.

Drying causes corneal opacities to disappear. When such corneas are rehydrated, the opacities do not reappear. Here, again, the effect

would seem to be one of rearrangement of the corneal fibers. The translucency of sclera on dehydration has the same significance as the clearing of corneal opacity on drying.

The sclera apparently becomes opaque in embryonic development as a result of its closely felted structure, which (1) does not permit dispersion of its fibers and free interchange of fluid constituents and (2) distorts the optic axis of the system of birefringence. Contrary to the conclusions of Cogan and Kinsey,[1] the difference in optical behavior between the cornea and the sclera has a "histologic counterpart," as is evident from the known differences in arrangement of the fibers in the two tissues, which, in turn, are reflected in the differences in swelling behavior.[2]

It is of importance to know that corneal opacities are reversible processes. Although it is a long way from these in vitro observations to therapeutic application, the first step has been made when the prevalent notion that ingrowth of fibroblasts dooms the cornea to permanent and irreversible opacity has been dispelled.

The scant hysteresis in corneal swelling suggests transplantation from stored material. It would be necessary, of course, to control carefully the rehydration of the dried tissue in order to insure transparent implants.

Studies on scattering of light in gelatin have no specific application to the ocular problem, but serve to demonstrate that one is dealing with similar phenomena in the matter of light transmission. The main variables affecting the light-scattering intensity in gelatin are temperature, the hydrogen ion concentration of the solution and the concentration of gelatin. Dhéré and Gorgolewski[6] found that purified gelatin solutions are strikingly turbid at temperatures below 30 C. Addition of acids or bases strongly diminished turbidity, as did warming to a temperature of over 30 C. These authors also found that scattering of light in gelatin is greatest at the isoelectric point. The cornea likewise shows greatest scattering of light at the isoelectric point, as well as the qualitative effects of change in acidity and variation in temperature, similar to those found for gelatin. The behavior of the cornea, however, is only analogous to gelatin, and differences are to be expected, since different specimens of gelatin will show specific characteristics. Lowering of temperature to 10 C. produces no noticeable change in the cornea except for a tendency for the maximum turbidity to shift from a p_H of 4.6 to one of 4.8. Increase in the temperature to above 40 C. produces marked optical improvement in the cornea, especially about the iso-

6. Dhéré, C., and Gorgolewski, M.: Recherches sur les propriétés chimiques de la gélatine démineralisée, J. de physiol. et de path. gén. **12**:645-656, 1910.

electric point. Dexter and Kraemer [7] reported that a change of a fraction of a p_H unit at the isoelectric point caused scattering of light in their specimen of gelatin to change as much as "1,000 per cent," a value which we presume to mean a tenfold change. We have not noted any such effect in the cornea.

Gerngross [8] found that neutral salts and nonelectrolytes, such as alcohol, urea and amino acids, diminish turbidity in gelatin, but to a less extent than do changes in acidity. Fischer [4] found that nonelectrolytes inhibit corneal opacity. We have found differences in the effects of the presence of certain electrolytes under the conditions of our experiments, as noted in the experimental results.

Sheppard and McNally [9] observed that when gelatin is stretched or otherwise deformed while being dried, subsequent swelling occurs anisotropically, the most rapid swelling being at right angles to the direction of deformity.

In summary, we find that the transmission and diffusion of light by the cornea are subject to the same chemical and mechanical influences as those which have been found for gelatin. Similarly, the anisotropy of the cornea is a function of its fibrous structure and lamellar arrangement. Its greatest swelling is at right angles to the direction of the axes of its fibers. The arrangement of the collagenous fibers in the fibrous tunic of the eye is believed to be fundamental in determining the optical difference between cornea and sclera.

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7. Dexter, E. O., and Kraemer, S. T.: The Light-Scattering Capacity (Tyndall Effect) and Colloidal Behavior of Gelatin Sols and Gels, J. Phys. Chem. **31**:764-782, 1927.

8. Gerngross, O.: Saürewirkung und H'-Konzentration bei Leim und Gelatine (unter besonderer Berücksichtgung der Trübungserscheinungen im isoelektrischen Punkt und der Gallertfestigkeit), Kolloid-Beihefte **40**:279-286, 1926.

9. Sheppard, S. E., and McNally, J. G.: The Structure of Gelatin Sols and Gels: II. The Anisotropy of Gelatin Gels, Colloid Symposium Monographs, Baltimore; Johns Hopkins Press, 1930, vol. 7, pp. 17-39.

HYPERCALCEMIA AND BAND KERATOPATHY

Report of Nineteen Cases

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ABNORMALITIES in serum calcium values have only recently been recognized to have ocular manifestations. The first reported observation is that of Meesmann (1938).[1] In his study on hypocalcemia Meesmann included a case in which band-shaped opacities of the cornea and opacities of the conjunctiva developed while the blood calcium was high. The cause of the hypercalcemia was overdosage with AT 10® (dihydrotachysterol), which the patient had been taking for hypoparathyroidism following thyroidectomy. The patient also had glaucoma, and Meesmann stated the belief that the primary cause of the opacities was glaucomatous dystrophy of Bowman's membrane, but he suggested that the hypercalcemia might have been a contributing cause and pointed out significantly that the opacities became less as the blood calcium was reduced to normal. Haldimann (1941)[2] described band-shaped opacities of the cornea in 2 patients with sarcoid and hypercalcemia. In view of the fact that the opacities developed in 1 patient before other evidence of sarcoidosis of the eye and in the other patient without ocular sarcoidosis at any time, Haldimann suggested that the hypercalcemia alone might be the responsible factor.[3] Walsh and Howard (1947)[4] reported a series of 16 cases, including a preliminary report of 7 of our series, in which hypercalcemia from a variety of causes was associated with opacities of the cornea and conjunctiva in otherwise normal eyes. These authors pointed out

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1. Meesmann, A.: Hypokalzaemie und Linse; ein Beitrag zur Behandlung der Tetanie und der Cataracta tetanica mit AT 10 Holtz, Klin. Monatsbl. f. Augenh. (supp.) **100**:1-66, 1938.

2. Haldimann, C.: Hornhaut- und Bindehautveränderungen bei Boeckscher Krankheit, Ophthalmologica **102**:137-145, 1941.

3. The systemic aspects presented by these 2 patients have been discussed elsewhere (Schupbach, A., and Wernly, M.: Hyperkalcämie und Organverkalkungen bei Boeckschen Krankheit, Acta. Med. Scandinav. **115**:401, 1943).

4. Walsh, F. B., and Howard, J. E.: Conjunctival and Corneal Lesions in Hypercalcemia, J. Clin. Endocrinol. **7**:644-652, 1947.

that conjunctival opacities also occur characteristically in association with hypercalcemia but that there was no correlation of the blood calcium level with either the corneal or the conjunctival opacities. Frost, Sunderman and Leopold [5] reported an additional case of calcific deposits in the cornea and conjunctiva resulting from prolonged overdosage with vitamin D. It is the purpose of the present report to describe our 19 cases (including the 7 previously incorporated in the report of Walsh and Howard [4]). This will make a total of 32 cases which have been reported to date. The importance of the subject is not great from the point of view of local functional disturbances produced by the opacities, since these rarely encroach on the pupillary area, but the findings do have correlative value in the diagnosis of systemic disturbances of calcium metabolism and may indicate what is taking place in the kidneys. Moreover, the fact that in hypercalcemia, calcium precipitates in the eye and has a characteristic distribution in the eye has interesting physiologic implications.

The ocular findings to be reported consist of subconjunctival opacities, variously described as white flecks or as glasslike crystals, and corneal changes, consisting of a diffuse superficial opacity in the palpebral fissure with a limbal margin that is usually abrupt and concentric with the limbus but is separated from it by a clear interval. The axial margin, on the other hand, fades away gradually a few millimeters centralward. The corneal changes are those generally called band keratitis, but, for obvious reasons, are more properly designated as band keratopathy. While the conjunctival opacities might be confused with calcification of the conjunctiva which occurs commonly without definite local or systemic disease, the band opacities in the cornea can be readily distinguished from the white limbal girdle and other opacities which occur "normally."

REPORT OF CASES

The following cases are grouped according to the etiologic factors in hypercalcemia.

HYPERPARATHYROIDISM

CASE 1.—M. C., a housewife aged 41, who complained of multiple tumors and fractures of bones of three years' duration, was referred to the hospital with the diagnosis of hyperparathyroidism. Because of increased serum calcium, low serum inorganic phosphorus and characteristic changes in bone, she had undergone four operations, with removal of parathyroid tissue each time. Nevertheless, her symptoms continued, and she sustained her last fracture while en route to the hospital! There were no ocular symptoms. Roentgenograms showed a staghorn renal calculus on the right, generalized skeletal decalcification, bone cysts, absence of the lamina dura and pathologic fractures.

5. Frost, J. W.; Sunderman, F. W., and Leopold, I. S.: Prolonged Hypercalcemia and Metastatic Calcification of Sclera Following Use of Vitamin D in Treatment of Rheumatoid Arthritis, Am. J. M. Sc. **214**:585-592, 1947.

Laboratory analyses showed the following serum values: calcium, 15.4 mg.; inorganic phosphorus, 3.6 mg.; alkaline phosphatase, 20.6 to 26.5 Bodansky units; nonprotein nitrogen, 37 mg., and total protein, 6.1 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2.6; carbon dioxide content, 22.5 to 24.4 milliequivalents. Urinalysis showed a negative to 3 plus reaction for albumin, 3 to 15 leukocytes and 0 to 40 red blood cells per cubic millimeter, abundant Escherichia coli, ability to concentrate to 1.016, 15 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 359 to 445 mg. of calcium in twenty-four hours.

Examination of the eyes showed a superficial corneal opacity concentric with the limbus in the palpebral fissure. It was separated from the limbus by a clear interval and extended axialward, to fade out approximately 3 mm. from the limbus. Examination of the conjunctivas was inadequate, since the patient could not be studied with the slit lamp biomicroscope, but there was a reflex from the surface of the conjunctiva resembling that from massed fish eggs.

At a fifth operation, a carcinoma of the parathyroid with metastases to the lymph nodes was partially removed.

Case 2.—P. G., a housewife aged 59, complained of generalized weakness, dyspnea, polyuria, polydipsia and swelling of the ankles. There were no ocular symptoms. Roentgenograms showed a ureteral stone, a duodenal ulcer and normal bony texture of the ribs and spine. Laboratory analyses showed the following serum values: calcium, 11.8 to 12.7 mg.; inorganic phosphorus 2.4 to 3.1 mg.; alkaline phosphatase, 1.6 Bodansky units, and nonprotein nitrogen, 23 mg., per hundred cubic centimeters; carbon dioxide content 23.8 to 28.1 volumes per cent. Urinalysis showed no albumin, an occasional leukocyte, inability to concentrate beyond 1.014 and 15 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed, in addition to unusually thin scleras, a superficial opacity on the nasal side of the cornea in the palpebral fissure, extending approximately 3 mm. from the limbus and separated from it by a thin, clear interval.

Adenoma of the parathyroid gland was removed at operation.

Case 3.—N. T., a farmer aged 62, complained of polyuria, polydipsia and painless swelling of the left side of the maxilla. There were no ocular symptoms. Roentgenograms showed nephrocalcinosis, generalized skeletal decalcification and several bone cysts. Laboratory analyses showed the following serum values: calcium, 15.2 to 17.3 mg.; inorganic phosphorus, 2.4 to 3.7 mg.; alkaline phosphatase, 8 to 14 Bodansky units; nonprotein nitrogen, 31 to 45 mg., and total protein, 5.9 to 7.7 Gm., per hundred cubic centimeters; carbon dioxide content, 16.8 to 27.9 milliequivalents. The urine showed a negative to a 3 plus reaction for albumin, numerous leukocytes, abundant Escherichia coli, inability to concentrate beyond 1.015, no excretion of phenolsulfonphthalein in fifteen minutes and excretion of 560 mg. of calcium in twenty-four hours.

The eyes were examined for the first time ten weeks after the operation. At that time there were numerous white opacities in the superficial conjunctivas, most of which were less than 1 mm. in size and resembled a flocculent precipitate. They could be seen only with a slit lamp. There was no band keratopathy, and the eyes were otherwise normal.

Biopsy of the tumor of the maxilla revealed epulis. At a second operation an adenoma of the parathyroid was removed.

Case 4.—E. K., a masseur aged 51, complained of tightness, stiffness and pain in the left calf. There were no ocular symptoms. A diagnosis of arteriosclerosis obliterans was made.

Twelve years previously he had been admitted with a diagnosis of hyperparathyroidism. Roentgenograms showed nephrocalcinosis and skeletal decalcification with bone cysts, two of which showed pathologic fractures. Laboratory analyses showed the following serum values: calcium, 16.8 mg.; inorganic phosphorus, 2.4 mg.; nonprotein nitrogen 32 mg., and total protein 5.7 Gm., per hundred cubic centimeters. Urinalysis showed 1 to 3 plus reaction for albumin, many leukocytes, an occasional red blood cell, Esch. coli, inability to concentrate beyond 1.018 and 5 to 15 per cent excretion of phenolsulfonphthalein in thirty minutes. An adenoma of the parathyroid was removed. The eyes were not examined at that time.

At the last admission laboratory analyses showed the following serum values: calcium, 11 mg.; inorganic phosphorus, 3.9 mg.; alkaline phosphatase, 3.9 Bodansky units; nonprotein nitrogen, 29 mg.; total protein, 6.7 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2; carbon dioxide content, 29.7 milliequivalents. The urine showed no albumin, 3 to 20 leukocytes per cubic millimeter and Esch. coli.

TABLE 1.—*Data on Patients with Hyperparathyroidism*

	Sex	Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.				Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Comment
				Calcium	Phosphorus	Phosphatase	Nonprotein Nitrogen	Amount, Mg./24 hr.	Stone			
	F	41	Multiple fractures	15.4	3.6	20.6-26.5	37	359-445	+	Marked decalcification; bone cysts; fractures	—	Carcinoma of parathyroid
	F	50	Weakness and polyuria	11.8-12.7	2.4-3.1	1.6	23	.....	+	No decalcification (ribs and spine)	+	Adenoma of parathyroid
	M	62	Epulis	15.2-17.3	2.4-3.7	8-14	31-45	560	+	Marked decalcification; epulis	..	Adenoma of parathyroid
	M	39	Multiple fractures	16.8	2.4	4.8-16.5	32	.....	+	Marked decalcification; bone cysts	—	Adenoma of parathyroid

* Data in table are those obtained prior to removal of the adenoma of the parathyroid, that is, twelve years prior to the present examination.

Examination of the eyes showed an arcuate gray opacity at the nasal periphery of the cornea. This was superficial, was concentric with the limbus, from which it was separated by a clear interval, and faded out gradually 1 to 2 mm. from the limbus. The changes in the eyes were slight but otherwise typical of band keratopathy. There was only one opacity of the conjunctiva, over the region of the external rectus muscle.

Of this series of 4 cases in which the cause of the hypercalcemia was hyperparathyroidism, band keratopathy with conjunctival deposits was present in 2, band keratopathy alone in 1 and conjunctival deposits alone in 1. One of the patients had carcinoma of the parathyroid with extension to the lymph nodes. The other patients had adenomas of the parathyroid, removed at operation.

The pertinent data in these 4 cases are summarized in table 1. From the diagnostic point of view the important findings were as follows: increased serum calcium, depressed or normal serum

inorganic phosphorus, elevation of phosphatase and characteristic decalcification of the bones, with cyst formation in 3 of the cases. But most interesting is the occurrence in all of either nephrocalcinosis or nephrolithiasis, for, as will be discussed subsequently in consideration of the pathogenesis of band keratopathy, the mechanism by which calcification occurs in the cornea may be similar to that by which it occurs in the renal tubules; indeed, one of the most important practical consequences of band keratopathy may be its implications regarding the presence of similar changes in the kidneys. Also noted in table 1 is the occurrence in some of the patients of duodenal ulcer, for, as will be indicated in some types of hypercalcemia, the coexistence of ulcer with the high calcium, high alkali diet appears to be of significance.

VITAMIN D POISONING

Case 5.—F. A., an engineer aged 27, complained of polydipsia and polyuria. For six years he had undergone extensive irradiation for generalized Hodgkin's disease. For four years he had taken 500,000 units of vitamin D a week for pruritus. The only ocular complaints were slight photophobia and burning of the eyes. Roentgenograms showed areas of increased density in the skull, spine and pelvis and miliary tuberculosis of the lungs. Laboratory analyses revealed the following serum values: calcium, 12.6 mg.; inorganic phosphorus, 4.3 mg.; alkaline phosphatase, 1.9 Bodansky units; nonprotein nitrogen, 52 mg.; total protein, 5.6 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.5; carbon dioxide content, 30.5 milliequivalents. The urine showed a negative to 1 plus reaction for albumin, 5 to 40 leukocytes and 0 to 4 red blood cells per cubic millimeter, cocci, ability to concentrate to 1.016, 15 per cent excretion of phenolsulfonphthalein in thirty minutes and excretion of 1,290 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band keratopathy, symmetric in the two eyes, which extended approximately 3 mm. from the limbus on both the nasal and the temporal side. It was visible to the unaided eye.

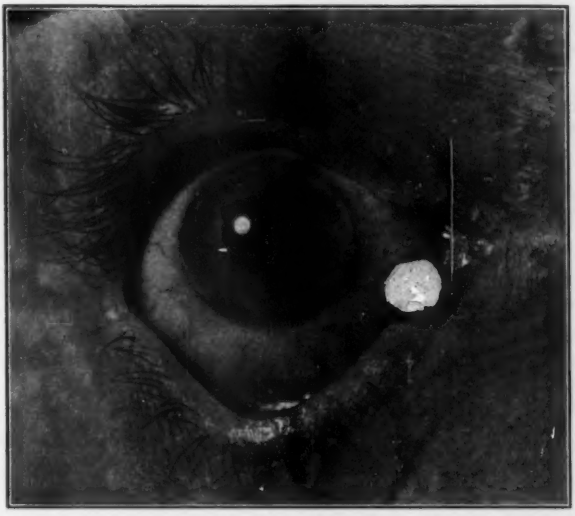
The patient died, and autopsy revealed nephrocalcinosis, miliary tuberculosis and Hodgkin's lymphoma.

Case 6.—E. B., a housewife aged 39, complained of abdominal pain, nausea, vomiting and swelling of the joints. For five years she had taken 100,000 units of vitamin D daily for rheumatoid arthritis. Roentgenograms showed a duodenal ulcer, extensive decalcification of the bones about the joints, periarticular calcification of soft tissues and no excretion of radiopaque dye in one hundred and five minutes. Laboratory analyses showed the following serum values: calcium, 10.2 to 14.4 mg.; inorganic phosphorus, 4.8 to 6.3 mg.; alkaline phosphatase, 3.3 to 7.4 Bodansky units; nonprotein nitrogen, 50 to 70 mg.; total protein, 7.0 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.15; carbon dioxide content, 21.4 to 24.9 milliequivalents. The urine showed a 4 plus reaction for albumin, 2 to 15 leukocytes per cubic millimeter, no organisms, inability to concentrate above 1.016, no excretion of phenolsulfonphthalein in fifteen minutes and excretion of 110 mg. of calcium in twenty-four hours.

Examination of the eyes showed superficial corneal opacities concentric with, but separated from, the limbus in the palpebral fissures, extending axialward about 3 mm. The conjunctivas also showed numerous fine opacities (presumably calcific) beneath the epithelium.

CASE 7.—A. M., a woman aged 70, complained of nausea, vomiting, diarrhea and depression. From eight to two months prior to admission she had taken 150,000 units of vitamin D daily for rheumatoid arthritis, from which she had suffered for fifteen years. She had consumed large amounts of milk. There were no ocular symptoms. Laboratory analyses revealed the following serum values: calcium, 11.7 to 13.9 mg.; inorganic phosphorus, 4.3 to 5.3 mg.; alkaline phosphatase. 4.0 Bodansky units; nonprotein nitrogen, 41 to 66 mg.; total protein, 7.5 to 8.2 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.1; carbon dioxide content, 21.4 milliequivalents. The urine showed a 1 to 3 plus reaction for albumin, 0 to many leukocytes and 0 to 30 red blood cells per cubic millimeter, no organisms, ability to concentrate to 1.017, 1 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 160 mg. of calcium in twenty-four hours.

Examination of the eyes without the aid of a slit lamp showed a definite band type of opacity in the palpebral fissure extending to 2 or 3 mm. from the limbus. No abnormality of the conjunctiva was to be seen grossly.



Photograph of the right eye of the patient in case 8. The paralimbal opacities can be seen as densest in the palpebral fissure and are characterized by an abrupt peripheral margin, bordering on a clear zone which separates it from the limbus and an axial margin fading out centrally 2 to 3 mm. from the limbus.

CASE 8.—T. C., a postal clerk aged 65, complained of vomiting and nocturia. For the past two to three years he had taken up to 300,000 units of vitamin D daily for rheumatoid arthritis. He consumed large quantities of milk. Recently several painless lumps had appeared in the skin of the neck, hands and wrists. The only ocular complaint was a mild foreign body sensation. Roentgenograms showed dense bones; calcification of soft tissues about the elbows, wrists and back, and rheumatoid arthritis. Laboratory analyses showed the following serum values: calcium, 11.6 to 15.2 mg.; inorganic phosphorus, 4.3 to 5.2 mg.; alkaline phosphatase, 4.4 Bodansky units; nonprotein nitrogen, 45 mg.; total protein, 7.32 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.25. The urine showed a negative to a 3 plus reaction for albumin, 0 to 30 leukocytes and 0 to 3 red blood cells per cubic millimeter, Staphylococcus albus, inability

to concentrate above 1.012, 5 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 445 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band type of superficial opacities in the palpebral fissure of both corneas, the band being separated from the limbus by a narrow, clear interval and extending axialward 3 to 4 mm. (figure). While the opacities were densest between 8 and 10 o'clock and 5 and 2 o'clock, some of the opacity extended down to 6 o'clock but none up to 12 o'clock. The peripheral portions of the opacity had many clear lacunas, presumably in areas corresponding to portions of the opacity which had sloughed off. The conjunctivas showed a follicular reflex from their surface temporal to the limbus, and with the biomicroscope there were several subepithelial crystalloid opacities.

CASE 9.—P. A., a woman aged 55, complained of "lumps" about various joints. There were no ocular symptoms. From four to one and a half months prior

TABLE 2.—*Data on Patients with Vitamin D Poisoning*

Patient No., Sex, Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.				Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Dose of Vitamin D, Units/Day	Comment
		Calcium	Phosphorus	Phosphatase	Nonprotein Nitrogen	Amount, Mg./24 Hr.	Stone				
5 M 27	Polydipsia; polyuria; pruritus	12.6	4.3	1.9	52	1,290	+	Increased density of spine, pelvis and skull	..	500,000 for 4 yr.	Tuberculosis; Hodgkin's disease
6 F 39	Epigastric pain	10.2-14.4	4.8-5.1	3.3	36-70	...	—	Metastatic calcification	+	100,000 for 5 yr.	Rheumatoid arthritis
7 F 70	Nausea; diarrhea; depression	11.7-13.9	4.3-5.3	4.0	80	100	—	Slight decalcification	..	150,000 for 6 mo.	Rheumatoid arthritis
8 M 65	Vomiting; nocturia	11.6-15.2	4.3-5.2	4.4	45	445	..	Excessive calcification in bone; metastatic calcification in skin	..	300,000 for 2-3 yr.	Rheumatoid arthritis
9 F 54	"Lumps" in soft tissues	13.4	5.7	5.9	62	125	—	Metastatic calcification in soft tissues	—	300,000 for 2½ mo.	Rheumatoid arthritis

to admission she had taken 300,000 units of vitamin D daily for rheumatoid arthritis, from which she had suffered for fourteen years. She had drunk 1 to 2 quarts (1 to 2 liters) of milk daily for several years. Painless lumps had appeared over one shoulder, both wrists and several fingers soon after she had started the vitamin D therapy. Roentgenograms showed normal bony texture; calcification of soft tissues about the hands, shoulders, back and knees, and rheumatoid arthritis. Laboratory analyses showed the following serum values: calcium, 13.4 mg.; inorganic phosphorus, 5.7 mg.; alkaine phosphatase, 5.9 Bodansky units; nonprotein nitrogen 62 mg.; total protein, 6.24 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2.22; carbon dioxide content, 26.6 milliequivalents. The urine showed a 2 plus reaction for albumin, 0 to 3 leukocytes and 0 to 12 red blood cells per cubic millimeter, inability to concentrate above 1.010, less than 5 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 125 mg. of calcium in twenty-four hours.

Examination of the eyes showed bilateral and symmetric opacification of the nasal and temporal portions of the paralimbal cornea in the palpebral fissure.

These opacities were superficial, were separated from the limbus by a relatively clear zone and did not extend more than 2 to 3 mm. axialward.

In this series of 5 patients with hypercalcemia and band keratopathy, 4 had taken excessive vitamin D on account of rheumatoid arthritis and 1 had taken it for pruritus. The dose of vitamin D varied from 100,000 to 500,000 units daily, and the time over which the vitamin was taken varied from two and a half months to five years. All the patients had renal insufficiency, as indicated by the nonprotein nitrogen and inorganic phosphorus levels of the blood, but it is noteworthy that the diagnosis of nephrocalcinosis was not evident roentgenographically, but was made only at autopsy on the 1 patient who died. It is entirely possible, therefore, that nephrocalcinosis was present in the other patients.

In contrast to the series of patients with hyperparathyroidism, those with excessive vitamin D intake showed no characteristic decalcification of the bones and no significant elevation in the serum phosphatase level.

SARCOID

CASE 10.—F. L., an engineer aged 25, complained of shortness of breath, loss of weight and productive cough. The only ocular symptoms were mild redness of the eyes and a feeling of dryness for the preceding several weeks. The patient's occupation had entailed exposure to beryllium silicate powder. Roentgenograms showed sarcoidosis of the lungs and increased density of the spine. Laboratory analyses showed the following serum values: calcium, 11.3 to 15.6 mg.; inorganic phosphorus, 3.0 to 3.6 mg.; alkaline phosphatase, 6.7 to 8.4 Bodansky units; nonprotein nitrogen, 26 mg., and total protein, 6.7 to 7.1 Gm., per hundred cubic centimeters. The urine showed a negative to a 1 plus reaction for albumin, 0 to 3 leukocytes per cubic millimeter, ability to concentrate to 1.020 and 40 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed slight ciliary and conjunctival redness. The corneas showed grossly an arcuate opacity of the cornea concentric with the limbus but separated from it by approximately 1 mm. The opacity was predominantly in the palpebral fissure but involved the lower portion of the cornea as well. With the slit lamp this opacity appeared entirely superficial and faded out axialward approximately 3 mm. from the limbus. On the scleral side of the limbus numerous superficial white lines radiated from the limbus but did not extend more than 1 to 2 mm.

CASE 11.—A. M., a housewife aged 36, complained of shortness of breath and cachexia. There were no ocular symptoms. Roentgenograms showed sarcoidosis of the lungs, renal stones, slight skeletal decalcifications and a fusiform area of calcification in the left buttock. Laboratory analyses showed the following serum values: calcium, 13.0 to 15.5 mg.; inorganic phosphorus, 2.9 to 3.8 Bodansky units; nonprotein nitrogen 26.5 to 75 mg.; total protein, 8.7 to 9.5 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 0.7; carbon dioxide content, 28.9 milliequivalents. The urine showed a 2 to 3 plus reaction for albumin, 5 to many leukocytes and 1 to 10 red blood cells per cubic millimeter, no organisms, ability to concentrate to 1.020, 10 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 433 mg. of calcium in twenty-four hours.

Examination of the eyes showed band keratopathy in both eyes, more pronounced on the nasal than on the temporal side. In addition to the diffuse granular opacities, the band contained several tiny opaque loops, simulating the configuration produced by obliterated vessels.

Biopsy of a lymph node, removed at operation, showed Boeck's sarcoid.

The patient returned seven years later. Laboratory analyses of the serum revealed calcium, 10.0 mg; inorganic phosphorus, 3.0 mg., and nonprotein nitrogen, 24 mg., per hundred cubic centimeters.

Examination of the eyes showed considerable reduction in the band keratopathy, with practically no residuum nasally and only a 1 mm. band temporally. There were, however, numerous subepithelial opacities of the conjunctivas adjacent to the temporal limbus.

The association of sarcoid with beryllium poisoning has been noted several times in the literature, and the first of these 2 cases has been previously included in a series illustrating this association.[6]

TABLE 3.—*Data on Patients with Sarcoidosis*

Patient No., Sex, Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.						Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Comment
		Calcium	Phosphorus	Phosphatase	Nonprotein Nitrogen	Protein	A/G	Amount, Mg./24 Hr.	Stone			
10 M 25	Shortness of breath and loss of weight	11.3-15.6	3.0-3.6	6.7-8.4	26	6.7-7.1	...	...	—	Increased density of spine	—	Sarcoidosis secondary to beryllium poisoning
11 F 36	Cachexia	13.0-15.5	2.9-3.8	2.9-3.7	26.5-75	8.7-915	0.7	433	+	Mild decalcification	—	Metastatic calcification in buttocks

One patient in this group showed impairment of renal function, as judged by the elevation of the nonprotein nitrogen and inorganic phosphorus levels of the blood, and at least 1 had nephrolithiasis. The changes in the kidneys and eyes, therefore, are similar to those resulting from excessive vitamin D intake.

UREMIA

CASE 12.—C. M., a clerk aged 49, complained of epigastric pain and shortness of breath. Five years previously he had had a sympathectomy for Buerger's disease (thromboangiitis obliterans). For twenty-five years he had taken large amounts of milk and alkali for relief of a duodenal ulcer. Roentgenograms showed a duodenal ulcer and normal bony texture. Laboratory analyses showed the following serum values: calcium, 11.4 to 12.8 mg.; inorganic phosphorus, 3.5 to 6.6 mg.; alkaline phosphatase, 2.2 to 3.1 Bodansky units; nonprotein nitrogen, 53 to 95 mg; total protein 6.81 Gm., per hundred cubic centimeters, with an

6. Hardy, H. L.: New Clinical Syndrome: Delayed Chemical Pneumonitis Occurring in Workers Exposed to Beryllium Compounds, Bull. New England M. Center **9**:16-24, 1947.

albumin-globulin ratio of 1.8; carbon dioxide content, 35.3 milliequivalents. The urine showed a 2 plus reaction for albumin, a few leukocytes, rare red blood cells, hyaline casts, inability to concentrate beyond 1.012, 7 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 109 mg. of calcium in twenty-four hours.

Examination of the eyes showed superficial opacities on the nasal and temporal sides of both corneas, of symmetric distribution in the two eyes. The opacity was chalk white and was densest toward the limbus, where it was slightly elevated and contained clear lacunas. It was separated from the limbus by a narrow, clear zone and faded off gradually axialward about 3 mm. from the limbus. It was more pronounced nasally than temporally. There were a few crystalloid, superficial opacities in the perilimbal conjunctiva and a follicular reflex from the conjunctiva in the palpebral fissure resembling that from massed fish eggs. Examination sixteen months later, showed that the ocular condition was unchanged.

Case 13.—A. C., a student aged 25, complained of protracted vomiting and emaciation. He had noted mild burning of the eyes. Roentgenograms showed periosteal formation of new bone; metastatic calcification in the tentorium, falx and bronchi, and small kidneys. There was no evidence of duodenal ulcer. Laboratory analyses showed the following serum values: calcium, 11.2 to 12.5 mg.; inorganic phosphorus, 4.4 to 4.8 mg.; alkaline phosphatase, 1.1 to 6.8 Bodansky units; nonprotein nitrogen 40 to 85 mg.; total protein 7.2 Gm., per hundred cubic centimeters; carbon dioxide-combining power 24.1 to 30.2 milliequivalents. The urine showed a 2 to 3 plus reaction for albumin, 0 to 6 leukocytes per cubic millimeter, inability to concentrate beyond 1.012 and 1 per cent excretion of phenolsulfonphthalein in twenty-four hours.

Examination of the eyes showed an abortive band type of corneal opacity concentric with the temporal limbus in the palpebral fissure. The adjacent conjunctiva was somewhat elevated and red and contained several subepithelial opacities.

The patient died three years later, without presenting further evidence of the fundamental cause of his disease.

Case 14.—V. Z., a housewife aged 23, complained of anorexia, nausea, vomiting, polydipsia and polyuria. She had avoided use of milk and alkalis. There were no ocular symptoms. The blood pressure was 190 systolic and 100 diastolic. Roentgenograms showed two calculi in the left ureter, slight decalcification of the spine, a normal lamina dura and poor renal excretion of radiopaque dye on the right and none on the left. Laboratory analyses showed the following serum values: calcium 13.2 to 13.4 mg.; inorganic phosphorus, 3.8 to 4.6 mg.; alkaline phosphatase, 1.8 to 2.6 Bodansky units, and nonprotein nitrogen, 40 to 45 mg., per hundred cubic centimeters; carbon dioxide content, 30 milliequivalents. The urine showed no albumin, a few leukocytes and red blood cells, a few alpha hemolytic streptococci, inability to concentrate above 1.012, excretion of 15 per cent of phenolsulfonphthalein in fifteen minutes and excretion of 187 to 413 mg. of calcium in twenty-four hours.

Examination of the eyes showed narrow bands of a superficial white opacity of irregular lacelike character situated on both the nasal and the temporal portion of the cornea of both eyes in the palpebral fissure. There were also many superficial irregular white opacities in the conjunctiva beneath the epithelium, but overlying the blood vessels.

Biopsy of two parathyroid glands showed secondary hyperplasia.

CASE 15.—A. M., a gardner aged 45, complained of weakness, nocturia and polydipsia. He had taken large amounts of milk and alkali for relief of a duodenal ulcer, from which he had suffered for many years. Five years previously he had passed renal calculi. For the past three years he had noted mild redness of the eyes. Roentgenograms showed renal stones, a duodenal ulcer and normal bony texture. Laboratory analyses showed the following serum values: calcium, 14.6 to 7.7 mg.; inorganic phosphorus, 4.0 to 9.4 mg.; alkaline phosphatase, 1.7 to 5.3 Bodansky units; nonprotein nitrogen 58 to 83 mg.; total protein 9.1 to 9.8 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.8; carbon dioxide content, 27.4 to 31.1 milliequivalents. The urine showed 2 to 40 leukocytes and 0 to 3 red blood cells per cubic millimeter, no organisms, inability to concentrate beyond 1.010, and 5 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed symmetric changes in the palpebral fissures in the corneas, consisting of slightly elevated white opacities concentric with the limbus, from which they were separated only by relative thinning, and extending axialward 2 to 3 mm., where they became nonelevated and apparently subepithelial. The opacities were situated on both the nasal and the temporal side of the corneas and were thought to be typical of band keratopathy. There were also yellowish and irregular plaques, measuring 4 to 5 mm. in diameter, situated, one each, in the nasal and temporal episcleras of both eyes. An attempt was made to remove one of these plaques for biopsy, but it was too firmly attached to the sclera and was left in situ.

The patient was kept under observation until he died in uremia six years later, during which time no evident change took place in his eyes.

Biopsy of two parathyroid glands, removed at operation, revealed a normal structure.

Autopsy showed nephrocalcinosis and calcification of the dura mater, respiratory diaphragm, costal cartilages, tendons and blood vessels.

CASE 16.—E. F., a stenographer aged 48, complained of pruritus and weakness. There were no ocular symptoms. Roentgenograms showed skeletal decalcification with bone cysts, osteoarthritis, a calcified deposit near the right elbow and contracted kidneys. Laboratory analyses showed the following serum values: calcium 8.8 mg.; inorganic phosphorus, 8.9 to 10.1 mg.; nonprotein nitrogen 140 to 155 mg.; total protein, 6.6 to 6.7 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.35; carbon dioxide content, 21.7 milliequivalents. The urine showed a 1 to 2 plus reaction for albumin, few leukocytes and red blood cells, no organisms, inability to concentrate beyond 1.012 and 5 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed a superficial opacity of each cornea on the nasal and temporal sides in the palpebral fissure, extending from the limbus approximately 2 mm. axialward, where it gradually faded out. No definite clear zone separated it from the limbus. Numerous tiny opacities also were situated just beneath the epithelium of the conjunctiva in the palpebral zone. These were placed superficial to the blood vessels and moved with blinking of the lids.

The patient died a few months later, without furthur examination.

CASE 17.—J. L., a fireman aged 52, complained of hematemesis. For many years he had taken large amounts of milk and alkali for relief of a duodenal ulcer.

Three years previously he had been admitted to the hospital with the complaint of a painful right eye. He stated he had had a "cataract operation" on the right eye as a child and that the vision had subsequently been poor. On this admission the following note was made: "Right eye was red, and practically the

entire cornea was infiltrated with calcium deposits. There was moderate ectasia. The chamber was deep. The pupil was small and immobile. The fundus reflex was absent. Tension was 3 plus. The left eye showed moderate but diffuse conjunctival redness and a marginal corneal opacity temporally and nasally from 2 to 5 o'clock and from 10 to 7 o'clock. The chamber, pupil and tension were normal." Because the glaucoma in the right eye was not relieved by miotics and the pain persisted, the eye was enucleated. Histologic examination of the cornea showed that the stroma and the posterior surface were not abnormal. Bowman's membrane was intact and appeared normal in its axial portion for an extent of 4 mm., but became increasingly calcified toward the periphery. At its limbal extremity the calcification of Bowman's membrane was densest and extended into the superficial stroma. Anterior to Bowman's membrane, and separated from it by a clear interval (an artefact), there was a new-formed membrane of lamellar stratification having a thickness about one-third that of the entire stroma. This new-formed membrane was composed for the most part of connective tissue with a variable amount of collagen and variable amount of hyalinization. At its periphery the membrane contained epithelium, which in the sections was not connected with the surface epithelium. In the anterior part of this new-formed membrane were calcific plaques, some of which were erupting through to the surface. These, like the calcification in Bowman's membrane, were more conspicuous toward the periphery of the cornea, where they could be seen extending through the whole thickness of the membrane. Also noteworthy were areas of calcification of the superficial half of the sclera in the region overlying the ciliary body. This was about 2 mm. in length on one side and involved one-half the thickness of the sclera and an area about 1 mm. in length on the other side and involved one-fourth the thickness of the sclera.

At the time of the present examination, roentgenograms revealed a duodenal ulcer, normal bony texture and no excretion of the radiopaque dye in forty-five minutes. Laboratory analyses showed the following serum values: calcium, 11.4 mg.; inorganic phosphorus, 4.7 mg.; alkaline phosphatase, 5.3 Bodansky units; nonprotein nitrogen, 80 to 105 mg.; total protein 6.8 Gm., per hundred cubic centimeters; carbon dioxide content, 21.8 milliequivalents. The urine showed a negative to a 1 plus reaction for albumin and inability to concentrate beyond 1.010.

Examination of the left eye showed a typical band-shaped opacity of the cornea in the palpebral fissure extending on the nasal and temporal sides from the limbal margin approximately 3 mm. axialward. The limbal edge of the opacity was irregularly scalloped and slightly raised, showing clear lacunas corresponding to portions of the opacity which had presumably been sloughed off. The opacity was entirely superficial. The conjunctiva showed grossly a follicular type of reflex in a 3 mm. zone temporal to the limbus and examination with the slit lamp biomicroscope revealed several subepithelial crystalloid opacities.

CASE 18.—E. M.,[7] a carpenter aged 55, complained of nocturia, pruritus and swelling of the legs. For twenty one months he had taken daily 4 to 5 quarts (4 to 5 liters) of milk and considerable alkali for relief of a duodenal ulcer. Physical examination showed movable subcutaneous nodules of the forearms. Roentgenograms showed calcification of the soft tissues of the extremities, and clubbing of the calyces was evident in retrograde pyelograms. Laboratory analysis showed the following serum values: calcium, 9.6 to 13.0 mg.; inorganic phosphorus, 3.7 to 5.9 mg.; alkaline phosphatase, 3.2 to 4.5 Bodansky units; nonprotein nitrogen,

7. Dr. Charles Burnett, of the Massachusetts Memorial Hospital, 65 East Newton Street, Boston 18, furnished the data on this patient.

80 to 100 mg.; total protein, 6.8 to 8.2 Gm., per hundred cubic centimeters; carbon dioxide–combining power, 24.0 milliequivalents. The urine showed a 1 to 2 plus reaction for albumin, occasional leukocytes and red blood cells, inability to concentrate beyond 1.011, less than 1 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 78 mg. of calcium in twenty-four hours.

Examination of the eyes showed a superficial opacity of the cornea in the paralimbal region of the palpebral fissure. It was present on both the nasal

TABLE 4.—*Data on Patients with Uremia*

				Laboratory Data, Mg. or Units/100 Cc.				Urinary Calcium				
Patient No.	Sex	Age	Present Complaint	Calcium	Phosphorus	Phosphatase	Nonprotein Nitrogen	Amount, Mg./24 Hr.	Stone	Roentgenographic Findings	Duodenal Ulcer	Comment
12	M	49	Epigastric pain	11.4-12.8	3.5-6.6	2.2-3.1	53-95	109	..	No decalcification	+	Intermittent claudication; much alkali and milk in diet
13	M	25	Vomiting 2½ yr.	11.2-12.5	4.4-4.8	1.1-6.8	40-85	.....	..	Calcification in bronchi and dura; periosteal new bone	—	Patient died; hyperparathyroidism not excluded
14	F	23	Vomiting; anorexia; polydipsia; polyuria	12.2-13.4	3.8-4.6	1.8-2.6	40-45	187-413	+	Mild decalcification	—	Two operations on parathyroid region showed secondary hyperplasia only
15	M	45	Weakness; nocturia; polydipsia	14.6-7.7	4.0-9.4	1.7-5.3	58-171	.....	+	No decalcification	+	Much alkali and milk in diet, no parathyroid adenoma found surgically or post mortem
16	F	48	Pruritus; weakness	8.8	8.9-10.1	.....	140-155	.....	—	Marked decalcification	..	Patient died a few months later
17	M	52	Hematemesis	8.3-11.4	3.9-4.7	4.4-5.3	65-109	.....	—	No decalcification	+	Much alkali and milk in diet
18	M	55	Nocturia; edema	9.6-13.0	3.7-5.9	3.2-4.5	80-100	78	—	Metastatic calcification in soft tissues	+	Much alkali and milk in diet
19	M	75	Urinary frequency	11.5-13.4	4.1-5.4	11.7-14.1	35-37	250-495	—	Osteitis deformans (Paget's disease)	..	Much milk in diet; hyperparathyroidism not excluded

and the temporal side, was about 4 mm. in length, was separated from the limbus by a narrow, clear interval and extended axialward about 2 mm. There were also scattered translucent bodies superficial in the conjunctiva extending 6 to 7 mm. temporal to the limbus and a few similar bodies extending nasalward.

CASE 19.—B. S., a fireman aged 75, complained of urinary frequency. For over a year he had taken daily 3 capsules containing a white powder. For several months he had taken 2 quarts (2 liters) of milk a day. There were no ocular symptoms. Roentgenograms showed generalized Paget's disease (ostitis defor-

mans) and good renal excretion of radiopaque dye. Laboratory analyses showed the following serum values: calcium, 11.5 to 13.4 mg.; inorganic phosphorus, 4.1 to 5.4 mg.; alkaline phosphatase, 11.7 to 14.1 Bodansky units; nonprotein nitrogen, 35 to 37 mg.; total protein, 6.1 Gm., per hundred cubic centimeters; carbon dioxide content, 30.6 milliequivalents. The urine showed a negative to a 2 plus reaction for albumin, 0 to 8 leukocytes and 0 to 3 red blood cells per cubic millimeter, no organisms, inability to concentrate beyond 1.010, 15 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 250 to 495 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band of keratopathy extending 2 to 3 mm. onto the cornea, without any definite clear zone separating it from the periphery. It was more pronounced on the temporal than on the nasal side. It was accompanied with three to four translucent crystals in the adjacent conjunctiva.

The cause of this patient's hypercalcemia and hyperphosphatemia with impaired renal function has not been determined. Differential diagnosis includes hyperparathyroidism, rapidly advancing osteitis deformans and the syndrome of Burnett and associates.[8]

From several points of view this group of cases is most interesting. They have in common uremia, band keratopathy and, with 1 exception, hypercalcemia. The etiologic factor was not apparent, but it is noteworthy that in at least 5 of them (cases 12, 15, 17, 18 and 19) high milk and high alkali diets had been taken for some time and the cases fall under the syndrome described by Burnett and associates,[8] in which renal damage (nephrocalcinosis?) is believed to result from high calcium and alkali intake. In 2 other cases in the series (cases 13 and 14) there was prolonged vomiting, and a nephrocalcinosis secondary to the chronic alkalosis may similarly have developed. The pathogenesis of the band keratopathy would presumably be the same as that of the calcification of the kidneys.

With the development of sufficient renal damage, the serum nonprotein nitrogen and inorganic phosphorus increase. But since the phosphorus and calcium levels of the blood tend to maintain reciprocal levels, the calcium which was originally abnormally high may fall to abnormally low levels as uremia supervenes. Thus, in case 15, when there was only moderate uremia, as indicated by serum nonprotein nitrogen of 80 mg., the calcium was 14.6 mg. and the inorganic phosphorus 4.7 mg. per hundred cubic centimeters, but when, toward the terminal stage, the serum nonprotein nitrogen had risen to 171 mg. and the inorganic phosphorus to 9.4 mg. per hundred cubic centimeters the calcium had fallen to the abnormally low level of 4.7 mg. per hundred cubic centimeters. We are not prepared to state to what extent band keratopathy may occur with renal damage and rising serum

8. Burnett, C. H.; Commons, R. R.; Albright, F., and Howard, J. E.: Hypercalcemia Without Hypercalcuria or Hypophosphatemia, Calcinosis and Renal Insufficiency: A Syndrome Following Prolonged Intake of Milk and Alkali, New England J. Med. **240**:787-794 (May 19) 1949.

inorganic phosphorus in cases in which there is not a preexisting hypercalcemia. Whereas the data on case 16 suggest that this change in the cornea may occur, the patient was first seen in the terminal stage of her disease, at a time when the serum nonprotein nitrogen and inorganic phosphorus levels were very high. The normal serum calcium may or may not have been preceded by a high level.

SUMMARY

Band keratopathy and calcification of the conjunctiva is reported in 18 cases of hypercalcemia and in another case in which the calcium level of the blood may be presumed to have been elevated previously. The hypercalcemia was due to hyperparathyroidism in 4 cases, to vitamin D poisoning in 5 cases and to sarcoidosis in 2 cases. In the remaining 8 cases it was associated with severe renal damage, owing, in some of the cases, to a high calcium and high alkali intake. The corneal opacity consisted of paralimbal opacification of the cornea extending 2 to 3 mm. axialward in the palpebral fissure. Many of the patients had nephrocalcinosis or nephrolithiasis, and the process occurring in the kidneys was thought to be analogous to that occurring in the cornea.

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DERMOID AND EPIDERMOID TUMORS OF THE ORBIT

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DERMOID and epidermoid tumors of the orbit are uncommon if the paraorbital growths or those located superficially in the eyelids are excluded. Of a series of 200 consecutive cases of exophthalmos reported in 1941 by one of us (R. L. P.),[1] instances of these congenital growths comprised 4 per cent. Constans [2] in 1943 collected from the literature 15 cases of cholesteatoma of the orbit and reported another; he stated that most of the tumors in his series should more correctly have been termed dermoids. Birch-Hirschfeld [3] in 1930 found 5 cases in the records of the Leipzig clinic. Samuels [4] in 1936, before this society, reported the histologic study of 13 dermoid cysts but failed to differentiate orbital from paraorbital growths. Many reports of isolated cases of oil, or dermoid, cysts affecting the orbit are to be found throughout the older and the more recent literature. When intraorbital these growths displace the eyeball, and it is they which we desire to discuss; we shall report a series of 9 cases and call attention to the characteristic defects in the bone of the orbit which these tumors produce and which may usually be recognized by roentgenography.

DIFFERENTIATION

Although the dermoid and the epidermoid are closely related in origin and behavior and require similar treatment, much has been

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1. Pfeiffer, R. L.: Roentgenography of Exophthalmos with Notes on Roentgen Ray in Ophthalmology, Tr. Am. Ophth. Soc., **39**:492, 1941; Am. J. Ophth. **26**:724, 816, and 928, 1943.

2. Constans, G. M.: Cholesteatoma of Orbit, Arch. Ophth. **30**:236 (Aug.) 1943.

3. Birch-Hirschfeld, A.: Das Dermoid des Orbita, in Graefe, A., and Salmisch, T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1930, p. 556.

4. Samuels, B.: Dermoid Cysts of the Orbit, Arch. Ophth. **16**:776 (Nov.) 1936.

written of their differentiation. The term epidermoid has replaced the older "cholesteatoma," or *tumeur perlée*[5] of the French, and is now in general use among neurologists, who have written most on the subject. The differentiation of dermoids from epidermoids seems academic. All the tumors are congenital rests from primitive ectoderm, and perhaps mesoderm as well, and the composition of each type depends simply on the time at which the cell rest developed, according to Boström,[6] or to the degree or depth of inclusion of the original dermal layer, according to Horrax.[7] Boström insisted that in the epidermoid growths all the tissue elements were derived from epithelial tissue. He regarded the dermoids, which contain mesoblastic structures, as arising from a dermis which differed not in actual depth of the original layer but in embryonic antiquity. A younger and more primitive cell layer, he suggested, will give rise to both epithelial and mesothelial tissues and the tumor will be characterized by a dermoid rather than an epidermoid type of growth. Both are primary epithelial tumors resulting from sealed inclusions, with the resulting structure depending on one of two factors. The depth of the primitive layer seems to be the critical factor, the epidermoid arising when the epidermoid tissue alone is concerned and the dermoid when the deeper, dermal, layer is in question. In either case, transitional types must and do occur commonly and make the differentiation unimportant. According to Critchley and Ferguson,[8] however, whose paper did most to clarify this subject, although there is little histologic or embryologic distinction between the dermoid and the epidermoid growths, there appear to be certain points of differentiation both clinically and anatomically. Thus, dermoid tumors produce symptoms earlier than do epidermoid tumors, are more likely to be multiple and often break down in the center to form cysts. In addition, the dermoid growth is more often associated with other congenital anomalies and developmental errors. These considerations assume little importance in the series of cases here reported. The ages of our patients ranged from 5 to 63 years, and the age distribution showed no significant relation to the type of growth except that the youngest patient had the only classic dermoid. All the

5. Cruveilhier, J.: Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible, Paris, J. B. Baillière, 1829, vol. 2, pt. 1, plate 6.

6. Boström, E.: Ueber die pialen Epidermoïde, Dermoïde, und Lipome und duralen Dermoïde, Centralbl. f. allg. Path. u. path. Anat. **1**:1897.

7. Horrax, G.: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, Arch. Neurol. & Psychiat. **8**:265 (Sept.) 1922.

8. Critchley, M., and Ferguson, F. R.: Cerebral-Spinal Epidermoid Cholesteatoma, Brain **51**:334, 1928.

tumors were single cystic lesions, unassociated with other known congenital anomalies.

Dermoids.—The orbital and intracranial dermoids vary from the size of a small seed to that of a large apple. They are encapsulated, are oval, round or hourglass in shape; their consistency is soft, usually cystic, and they are opaque, yellow or brownish, the color depending on the presence of hemosiderin. If the tumor is cystic, the content is fatty, soapy, flaky or crumbly. The presence of sebaceous material, fat and cholesterol crystals, in varying proportions, determines the consistency of the mass, and the tumor always contains hairs, coiled, clumped or matted together. The presence of hair has been regarded as pathognomonic of the dermoid. Boström, Horrax and others, however, have recorded cases of epidermoid cysts in which hair was found, and such growths may thus be regarded as transitional. A low grade inflammatory reaction was manifest in the walls of most dermoids.

Microscopically, the constituents of dermoid tissue resemble those of skin, and one can distinguish, from without inward, a fibrous, outer layer; a connective tissue stroma (corresponding to the corium), and an epithelial, inner layer. Blood vessels may be seen in the connective tissue layer, especially at the site of the dermoid tuft, which represents the location of the original dermal implantation and the place of greatest growth. In addition, this layer may contain sebaceous glands, hair follicles, fat cells, smooth muscle and elastic fibers. Deposits of calcium and cartilaginous spicules may also be seen in the connective tissue matrix.

The epithelial, inner layer, a purely ectodermal derivative, varies greatly in thickness, consisting sometimes of a single layer of cells and at others of a stratification similar to that of skin, with germinative, granular and cornified layers. As in normal skin in which there are a number of layers of cells, the innermost ones have the more flattened or polygonal cells, and in these layers the nuclei disappear, the cells become horny and keratohyalin bodies and cholesterol crystals (the end products of epithelial disintegration) occur.

In the main cavity of the dermoid cyst, varying amounts of hair, sebum, cholesterol and oil are present. This material may be rancid and toxic and may be irritating and produce evidence of inflammation in the cyst or in neighboring tissue. A tooth was found in Borley's [9] case. Samuels found the epithelial layer incomplete in some cysts and observed little tendency of the epithelium to proliferate in filling in defects. Such defects are found associated with the inflammatory reaction. He observed cellular and granulation tissue undermining the epithelium and, in the deeper layers of the wall, nodules of epithelioid

9. Borley, W. E.: Dermoid (Oil) Cyst of Orbit, Am. J. Ophth. **22**:1355, 1939.

or giant cells. According to Samuels, the so-called oil cysts show a predominance of sebaceous glands. Vassaux and Broca [10] expressed the belief that the oil represented degenerated fat cells, but this statement is not borne out by chemical analysis and histologic observation. Knapp's [11] case, reported before this society, is noteworthy for the chemical examination of the content of the cyst. Jones [12] reported a case of an oil cyst which became malignant, the patient dying of carcinomatosis. It is probable that the so-called blood cysts are dermoid cysts in which hemorrhage has occurred and in which, because the entire cyst could not be examined, an epithelial lining was not found.

The histologic study of these large growths leaves much to be desired. Because of the technical difficulties at operation, only fragments of the wall of the cyst, along with some of the content, can be offered for study. Study of the smaller paraorbital dermoids is only indicative of the structure of these large growths, which have been subject to pressure influences from within and from without and to impoverished circulation, perhaps, with degeneration occurring within, forming toxic substances which react on the mother tissue. Most of the smaller paraorbital growths, with the solid mass of epithelial products within (often mistaken for sebaceous cysts), are good examples of epidermoid cysts).

Epidermoid.—This simpler tumor forms a solid mass which may be described as being made up of two concentric layers of different thicknesses, forming the capsule, and a main, central mass, making up the bulk of the tumor. The outer layer, or stratum durum, which gives the tumor its nacreous sheen, may be thin or so thick as to constitute a tough, fibrous envelope. It is composed of layers of collagen fibers, with little or without cellular formation. Beneath the stratum durum lies the characteristic layer, which constitutes the histologic criterion of the epidermoid cyst. The stratum granulosum, as it is called, is essentially a cellular layer of epithelial cells, which varies in thickness from one or two cells, as is usually the case, to ten or more layers of cells, the layers varying in character according to their depth. Fine granules composed of keratohyalin are scattered throughout the cytoplasm of these cells. The interior of the tumor is composed of the accumulated products of the desquamated epithelial layer, which appears in loosely packed layers of wavy, homogeneous laminas, with numerous flat cholesterol crystals. This tumor is completely avascular, and the content is nonvital.

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10. Vassaux, G., and Broca, A.: Contribution à l'étude des kystes à contenu huileux, Arch. d'opht. **3**:318, 1883.

11. Knapp, A.: Oil Cyst of Orbit, Arch. Ophth. **52**:163 (March) 1923.

12. Jones, A. C.: Oil Cyst of Orbit with Carcinomatosis, Am. J. Ophth. **18**: 532, 1935.

The nomenclature of the epidermoid tumors has caused considerable confusion. The term cholesteatoma is not applicable. Because cholesterol does not play an essential role in the histology of these growths and is found in a great variety of tumors, the use of this name should be discontinued. The indispensable criterion for the diagnosis of epidermoid growths is the microscopic demonstration of epidermoid elements making up the wall of the tumor. One is logically bound to name the growth from its essential feature, and the term suggested by Critchley and Ferguson, that is, epidermoid, should be used. But, in view of the close relation of this tumor to the dermoid, one may well question the propriety of making the distinction. The term dermoid seems adequate.

Something should be added to distinguish the congenital epidermoid cyst from the cholesteatoma associated with disease of the middle ear. The latter lesions, associated with infection of the middle ear cavity, consists mainly of epithelial debris with fat, granulation tissue, leukocytes and cholesterol crystals and may be simply the accumulated products of excessive desquamation and reaction to inflammation (cholesteatosis). Erdheim,[13] Lucae[14] and Kuhn,[14] however, reported typical epidermoid cysts in the middle ear unassociated with infection. It may be that under the stimulus of the inflammatory process the backgrowth of the meatal epithelium through the tympanic cavity gives rise to dermoid formation. It is possible, on the other hand, that the tumor may be present in the middle ear as an epithelial rest and that its presence predisposes the ear to suppuration, so that infection and tumor formation are discovered in association with each other.

Present Series.—Most of the cases described here had characteristics of both the dermoid and the epidermoid. Only 1 tumor of our series contained hair (case 8). All the growths were cystic and contained a brown, oily fluid, with cholesterol and hemosiderin and sometimes masses of yellowish debris. All had fibrous walls, of variable character, with epithelial lining. In many cysts blood vessels were revealed at operation and on section. Low grade inflammatory reaction was manifest in the walls of most of the tumors.

In all but 1 of these cases (case 8) the tumors appeared to be intermediate or transitional types arising either from deep, or early, or from superficial, or late, epithelial rests. The oil content must be recognized as evidence of the presence of sebaceous glands, though these structures were not conspicuous in the walls of most of the tumors. The blood vessels attest to the depth of the layer and the presence of a mesodermal constituent in the original cell rest. The absence of

13. Erdheim, J.: Ueber Schädelcholesteatoma, Ztschr. f. Ohrenh. **49**:281, 1905.

14. Cited by Critchley and Ferguson.[8]

hair, however, indicates the superficiality of the epithelial rest. The brown or chocolate color of most of the tumors was due to the hemosiderin content and indicated that bleeding had occurred, probably as a result of the toxicity of the content and the secondary inflammatory reaction, with rupture of vessel walls. The epithelial layer in all 8 cases was extremely thin, and the great masses of cholesterol were common to both types.

The case of Rasquin,[15] that of a multilocular dermoid of the orbit in which one portion was an oil cyst and another a solid epidermoid (though he called it a sebaceous cyst), is evidence of the relation of dermoid and epidermoid cysts.

We have encountered no reference in the literature to the possibility of epidermoids undergoing degeneration with liquefaction. It would seem that these tumors maintain their solid form, even though they reach massive proportions and are without blood vessels. Although a nonvitalized growth, they seem not to become toxic. The case of King[16] (case 4 in his series), in which a very large cyst involving the orbit was filled with thick, viscid, olive-green material of the consistency of coal tar, together with semifluid, opaque masses, most nearly suggests a combination of dermoid and epidermoid constituents. King attributed this odd situation, however, to a communication with the ethmoid and/or frontal sinuses. In none of our cases did the cysts communicate with the sinuses. The content of retention cysts, or mucoceles, arising in a paranasal sinus is altogether different from that of a dermoid cyst and need not be confused.

ROENTGENOGRAPHY

The dermoids or epidermoids may arise in the diploe of the skull or bones of the orbit and in their growth expand both the inner and the outer table and produce rather characteristic defects. They may arise subperiosteally or subperiorbitally and produce fossae or indentations of the bone with typical markings. These defects, whether fossae, dehiscences or openings in the bone, may be demonstrated roentgenographically and may serve to indicate the nature of the process and, in case of involvement of the orbit, the cause of the resulting exophthalmos.

In the older literature, defects in the bone of the orbit associated with dermoids discovered at operations were mentioned by Doyne,[17]

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15. Rasquin, E.: Kyste dermoïde multiloculaire interne de l'orbite à contenu huileux, Bull. Soc. belge d'opht. **64**:78-80, 1932.

16. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), Ann. Surg. **109**:649, 1939.

17. Doyne, R. W.: Dermoid Tumor of Orbit, Ophth. Rev. 1896, p. 97.

Chevallereau,[18] Cant[19] and Krönlein.[20] Since the discovery of the roentgen ray more frequent mention of orbital changes may be noted (Pincus,[21] Michail,[22] Varona,[23] Kreibig,[24] Panneton and Roux,[25] Constans[2]). No special attention had been given, however, to the bony defects as a possible means of diagnosing dermoid of the orbit. Our series of 9 cases, which comprises all the verified cases of dermoids and epidermoids which we have seen, may well illustrate the importance and nature of the bony involvement in the diagnosis and treatment of these growths. In addition, 5 more unmistakable cases have been studied, but have not as yet been verified histologically and are not considered in this paper.

In their most typical form, the defects in the bone of the orbit produced by these congenital growths are revealed in roentgenograms by sharply demarcated margins, with increase in the density of the bone at the margin, and diminished tissue density within the confines of the lesion itself. In the first case such studies revealed a bean-shaped fossa in the lateral wall of the orbit, and in the second case, a bean-shaped hiatus or dehiscence in the roof of the left orbit, with the features mentioned. The next 3 cases illustrate different stages in the development of dermoids in the roof of the orbit near the zygomatic process of the frontal bone. Case 6 demonstrates the startling size which one of these lesions may attain. This case is remarkable in the thickness and density of the bone in the wall of the cyst. The diminished soft tissue density and the increased radiolucency of the growth are due to the oil and/or cholesterol content. When associated with dehiscence of the bone, with calcium of the bone therefore lacking, the dark appearance of the growth is striking in the roentgenogram.

In the present series, the frontal bone was involved in 7 of the 9 cases. In 6 of these 7 cases the growth appeared to have arisen in the diploe of the bone forming the roof of the orbit. In cases 2 and 9 a through and through defect in the bone was produced, so that pulsation of the dura was observed at operation. An hourglass tumor

18. Chevallereau, A.: Kyste dermoide à parois osseuses et à contenu piérreux, Soc. d'opht. **5**:1, 1892.

19. Cant, W. J.: Cyst of Orbit, Ophth. Rev. 1896, p. 187.

20. Krönlein, R. U.: Zur Pathologie und operativen Behandlung der Dermoidcysten der Orbita, Beitr. z. klin. Chir. **4**:149, 1889.

21. Pincus, F.: Ueber "Cholesteatom" der Orbita, Klin. Monatsbl. f. Augenh. **90**:145, 1933.

22. Michail, D.: Cholestéatome de l'orbite, Arch. d'opht. **48**:743, 1931.

23. Merino, Varona, A.: Presentación de un caso de colesteatoma de la órbita, Rev. de méd. y cir. de la Habana **42**:687, 1937.

24. Kreibig, W.: Zur Kenntnis seltener Orbitaltumoren, Ztschr. f. Augenh. **95**:113, 1938.

25. Panneton, P., and Roux, R.: Un cas très rare de cholesteatome de l'orbite, Union méd. du Canada **70**:812, 1941.

was found in case 7, with portions both in the frontal fossa and in the orbit. The largest tumor (case 6) appeared to have arisen in the diploe of the roof and to have grown upward mainly, to occupy most of the frontal fossa of that side. In case 8 the tumor arose subperiorbitally to deform the upper portion of the orbit and did not give rise to the common dehiscence or fossa in the bone. In several cases the adjacent frontal sinus was encroached on, but in all cases these sinuses were

Clinical Data on 9 Cases of Orbital Dermoid with Exophthalmos

Case	Age, Yr.	Sex	Duration of Symptoms	Exophthalmos, Mm.	Roentgenographic Findings	Follow-Up Period; Outcome
1	11	M	1½ yr.	7	Circumscribed bean-shaped fossa in lateral wall of right orbit with diminished density	15 yr.; no recurrence
2	38	F	1 yr.	4	Circumscribed kidney-shaped hiatus in roof of left orbit with diminished density	1½ yr.; no recurrence
3	38	M	2 yr.	7	Well defined cystlike lesion in right frontal bone above zygomatic process	5 yr.; no recurrence
4	40	F	4 mo.	4	Deep fossa in frontal bone, extending up anteriorly from orbit with diminished density	3 yr.(?); no recurrence
5	63	M	5 yr. Recurrence 15 yr. after operation	11	Similar to findings in case 4	3 yr.; no recurrence
6	18	F	2 yr.	12	Massive cystic lesion with calcified walls occupying much of right frontal fossa and half of orbit	6 mo.; will recur, incomplete removal
7	47	M	6 yr.	20	Large mass of increased density occupying defect in left frontal bone, much of orbit and encroaching on frontal sinus with fossa in lateral wall of orbit	2 yr.; no recurrence
8	5	M	5 yr.	5	Enlargement of right orbit above, without typical appearance of dermoid	3 mo.
9	50	M	18 mo.	9	Oral hiatus in bone with sharp margin of increased density and diminished density of lesion itself	15 yr.; no recurrence

clear and the wall of the growth could be well distinguished. In the first and seventh cases the growth affected the lateral wall of the orbit or the greater wing of the sphenoid bone. In both cases it appeared as though the lesion arose from a subperiorbital rest. In case 7 a tremendous tumor had arisen entirely within the orbit, associated with a small, nearly circular, dehiscence in the lateral wall beneath the sphenoid ridge. This opening in the bone should have indicated clearly the nature of the lesion in spite of the increased density of the shadow on the film, which was due to the high blood and/or hemosiderin content of the mass.

In differential diagnosis, several conditions must be considered. Retention cyst or mucocele of the frontal sinus may resemble a dermoid but may be distinguished by its connection with the sinus and the clouded condition of the sinus itself, together with absence of the characteristics of the dermoids previously given. A xanthoma of the bone or an eosinophilic granuloma may suggest a dermoid, but in such cases the criteria for dermoids are not satisfied, especially in respect to the increase in the density of the bone at the margins of the lesion. Invasion by a malignant tumor may have to be differentiated. Some resemblance was produced by a meningioma of the sphenoid ridge in a boy of 16, and this tumor, therefore, should be considered as capable of offering difficulty in differentiation. Meningocele may be confused with dermoid. The commonest site of this congenital opening in the bone is at the root of the nose, and it is indeed extremely rare (we have but 1 meningocele in our great collection of material). Saccular aneurysms of the internal carotid artery often erode the bone of the apex of the orbit and may also simulate a dermoid.

REPORT OF CASES

CASE 1.—*Dermoid (Oil Cyst), Subperiosteal of Right Orbit, Causing Exophthalmos. Fossa in Lateral Wall Revealed by Roentgenogram. Preoperative Diagnosis of Dermoid. Operation, With Removal of Cyst. No Recurrence After Fifteen Years.*

H. B., a school boy aged 11, had had varying degrees of prominence of the right eye for the past one and a half years, without other symptoms. Vision was normal. There was no diplopia or muscular imbalance. Exophthalmos of the right eye measured 7 mm., with the eye displaced solidly forward. There was 1 mm. of papilledema in this eye.

Roentgenographic examination disclosed a sharply circumscribed, bean-shaped defect or fossa measuring approximately 15 by 30 mm. in the lateral wall of the right orbit between the superior orbital (sphenoid) fissure and the temporal line. The bone of the margins showed increased density, and the area within the confines of the margins revealed diminished density, suggesting an oil content. The bone of the floor of the indentation was extremely thin, but no dehiscence could be seen. All the paranasal sinuses were clear; the left orbit was normal; the optic canals were circular and symmetric and the calvaria was normal. The impression was that of a dermoid of the right orbit.

Operation (Dr. J. M. Wheeler).—Through an incision through the lateral canthus, a brownish mass was revealed in the lateral wall of the right orbit; the orbit was rather soft but had a firm ridge of elevated bone at its base. In an attempt to loosen the growth, the wall ruptured, and a large quantity of brown, greasy fluid with cholesterol crystals was liberated. The interior of the remaining sac was phenolized and washed with alcohol, after which as much as possible of the thin, friable wall was removed. The wound was closed with silk sutures, and a pressure dressing was applied. The course of recovery was uneventful.

Pathologic Examination.—The specimen consisted simply of a bit of lacrimal gland which had inadvertently been removed. The tissue showed infiltration with leukocytes, plasma cells and reticulum cells, with numerous capillaries.

Subsequent Report.—A follow-up examination fifteen years later disclosed no abnormality of the eyes.

Comment.—This case is a fine example of a dermoid, or oil cyst, of the orbit. The roentgenologic appearance was typical, and the treatment was definitive. It is probable that the exophthalmos had been present for several years before it was noticed by the parents. The inflammation revealed by the tissue of the lacrimal gland suggests the irritating nature of the cyst content.

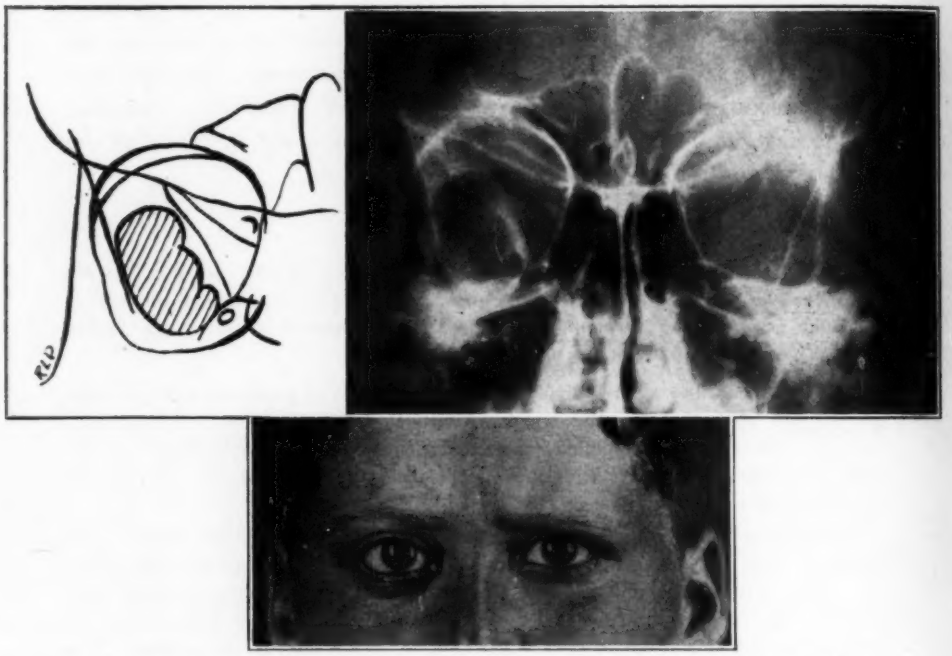

Fig. 1 (case 1).—Subperiorbital dermoid (oil cyst) of right orbit, producing a bean-shaped defect in the lateral wall, with characteristic roentgenographic findings.

CASE 2.—*Intradiploic Dermoid of Roof of Orbit, Involving Frontal Fossa and Producing Exophthalmos. Characteristic Defect of Bone as seen in Roentgenogram. Frontal Osteotomy and Removal of Growth.*

M. F., a white woman aged 36, had complained of periodic frontal headaches for many years; the attacks were brought on by dietary irregularities and were relieved by sleep. The left eye began to bulge eight months before her admission, and the exophthalmos had been increasing, without loss of vision and without double vision. This eye was observed to show 4 mm. of exophthalmos and to be displaced slightly inferiorly. Double vision could not be shown. Neurologic examination revealed nothing else of significance.

Roentgenographic examination disclosed a kidney-shaped defect in the roof of the left orbit, measuring approximately 1.5 by 3 cm. with sharp margins and a pronounced increase in the density of the surrounding bone. The area of the defect, or hiatus, showed striking diminution in tissue density. The left frontal sinus was small and uninvolved. All the paranasal sinuses were clear. The impression was that of a dermoid involving both the left orbit and the anterior cranial fossa.

Operation (Dr. Charles A. Elsberg, of the Neurological Institute).—Frontal flap was placed close above the left orbit, and a cystic cavity was opened as soon as the flap was raised. A great quantity of dark brown fluid was released from a large cystic cavity lying beneath the left frontal lobe, under and adherent to the dura and extending through a large defect in the roof of the orbit, to connect with a cystic recess within the orbit itself. The brownish fluid was full of cholesterol

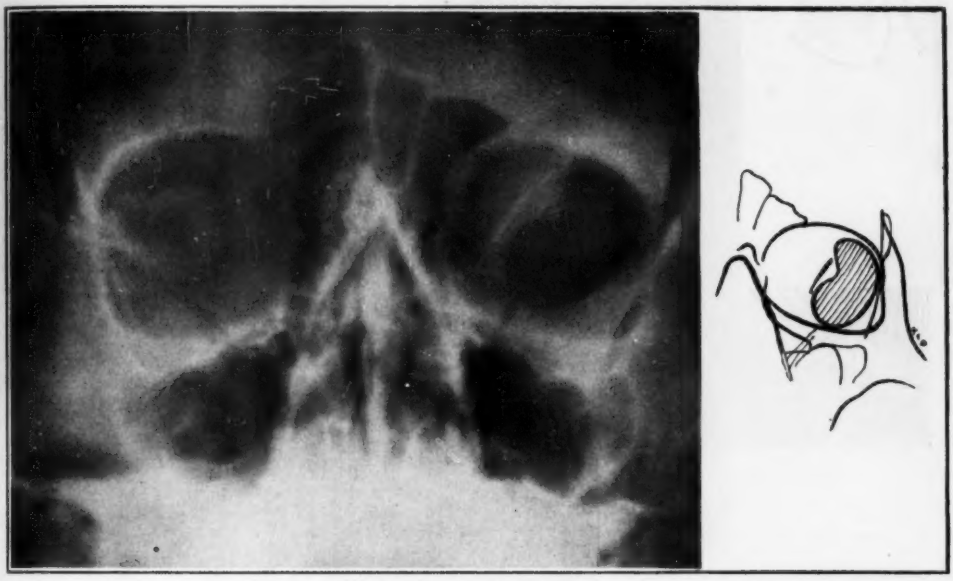

Fig. 2 (case 2).—Intradiploic dermoid of the roof of the left orbit, producing a defect in the bone, through which the intracranial and the orbital portion of the growth communicated.

crystals. Several pieces of the cystic wall were removed, after which the cavity itself was thoroughly treated with Zenker's solution. Most of the cystic wall was excised, and at no time was the dura penetrated.

Pathologic Examination.—Specimens of the wall of the cyst consisted of heavy masses of hyalinized connective tissue, containing slits produced by the solution of cholesterol crystals. Squamous epithelium of a papillary type was evident and probably formed the lining membrane of the growth. No blood vessels or hair was in evidence. The diagnosis was epidermoid.

Comment.—This growth probably arose from a diploic epidermal rest and, because of the absence of blood vessels, hair, and other dermal structures and because of the concentrated content, should be regarded

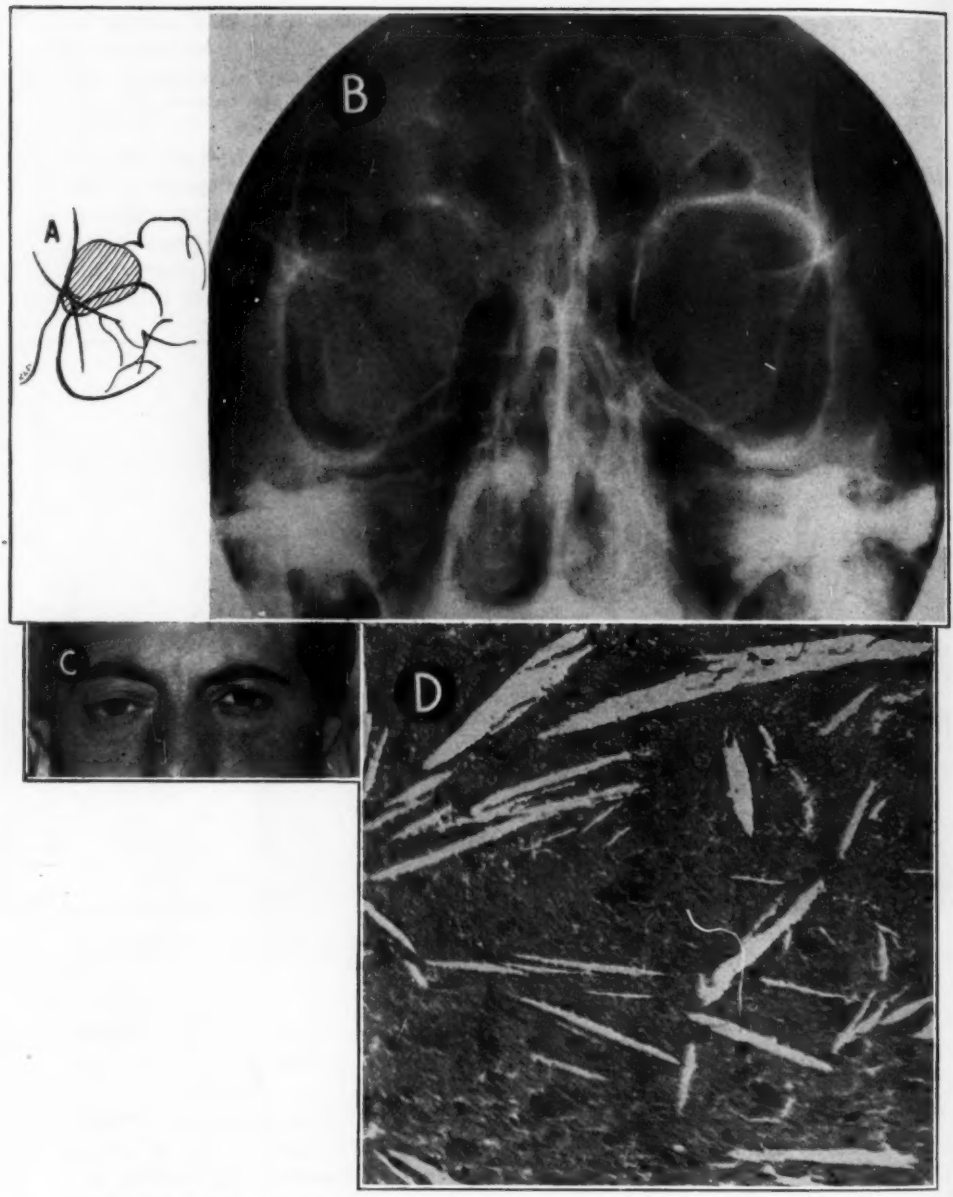

Fig. 3 (case 3).—Intradiploic dermoid of frontal bone, revealing roentgenographic characteristics of circumscribed margin with increased density of bone at the margin and diminished density of the growth itself. Note calcium in wall of the cyst bulging into orbit. *D* shows cholesterol crystals in amorphous contents of the cyst. See description in text.

as an epidermoid. The tumor was of especial interest because of the dumb-bell shape, with one portion in the orbit and the other within the cranium and external to the dura mater.

CASE 3.—*Dermoid, Intradiploic, in Roof of Right Orbit, Causing Exophthalmos. Cystic Defect Revealed Roentgenogically. Preoperative Diagnosis: Dermoid. Operation and Removal of Cyst.*

D. R., a white man aged 38, a plumber by trade, had had increasing exophthalmos of the right eye for two years. There were no other symptoms or complaints. Vision was normal, with correction, and there were no field defects or changes in the fundus. The right eye was displaced solidly outward and downward, with exophthalmos measuring 7 mm. There was left hypertropia, which increased with the eyes looking up and to the right.

Roentgenographic examination revealed a cystlike defect, measuring 2.5 by 3 mm., in the roof of the right orbit above the zygomatic process and fossa for the lacrimal sac, with sharply circumscribed margins and some increase in the density of the bone at the margins. The lower extent of the lesion was revealed in the orbit by calcium in the capsule or wall. The area within the margins showed diminished density of the tissue, suggesting oil or fat. This cystic lesion

Fig. 4 (case 4).—Diploic dermoid of frontal bone of left side deforming orbit and producing severe exophthalmos.

did not connect with the right frontal sinus, which lay adjacent and which appeared indefinitely clear. The impression was that of dermoid cyst of the roof of the right orbit.

Operation (Dr. R. L. Pfeiffer).—Through an incision made over the outer half of the superior margin of the orbit down to the bone, the periorbita was elevated and dissected back to expose a firm, bulbous, brown mass. This mass was opened to liberate a large quantity of oily fluid with semisolid, yellowish material, which glistened. The sac was cleaned out thoroughly and treated with phenol and alcohol, after which the lower wall was removed with as much of the lining as could be stripped away. The wound was closed tightly and a pressure dressing applied. Healing was uninterrupted.

Microscopic Examination.—The specimen consisted of a fragment of the cyst wall. This was composed of connective tissue in which there were many spaces occupied by cholesterol crystals, some bone formation, old hematogenous pigment and some lymphocytic infiltration. There were a number of foreign body giant cells, which appeared mostly in relation to the sites of the cholesterol crystals. There were only faint suggestions of epithelial remnants, and no gland structures or hair follicles were noted. The diagnosis was degenerative changes incident to a dermoid cyst.

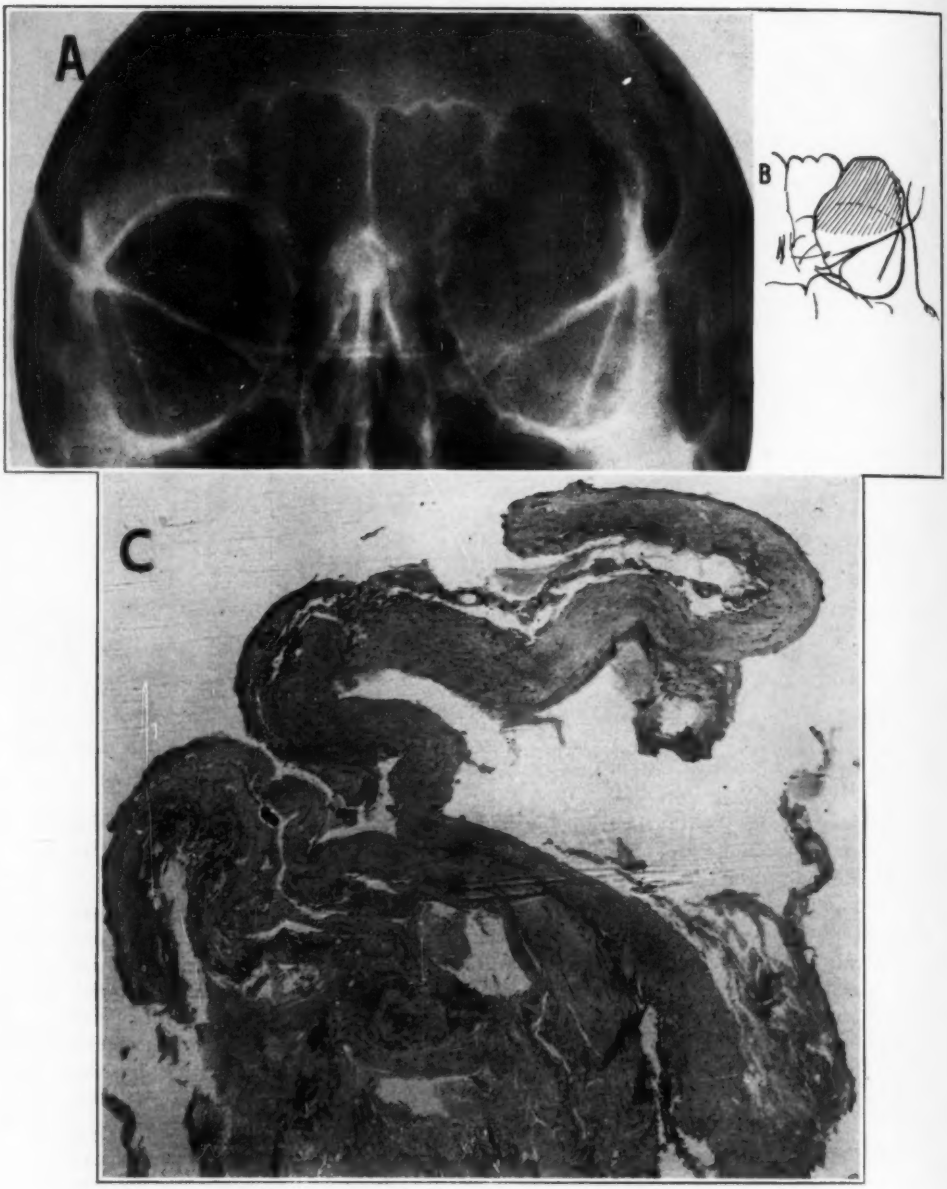

Fig. 5 (case 4).—Diploic dermoid of left frontal area. The inferior limit of the cyst is not visible roentgenographically. *C* shows portion of wall of cyst under low power magnification.

Comment.—There was no evidence of recurrence after an interval of five years.

CASE 4.—*Dermoid, Diploic of Left Orbit, Causing Exophthalmos. Large Defect or Fossa in Roof of Orbit Shown in Roentgenogram. Preoperative Diagnosis: Dermoid. Operation, With Removal of Cyst.*

D. P. A., a married white woman aged 40, had had partial ptosis of the left upper eyelid since a sinus infection eight years earlier. The eyeball began to protrude four months prior to admission, and exopthalmos measured 4 mm. There was no discomfort or diplopia. Vision was normal with correction. The fundi were normal. A mass was palpable above, displacing the eye downward and outward.

Roentgenographic examination revealed a large excavation or fossa in the roof of the left orbit with sharp margins, slight increase in bone density at the margins and diminished density of the lesion itself. This fossa measured approximately 2 by 3 cm. and lay adjacent to the frontal sinus, on which it encroached but with which it did not connect, since a well defined wall of the cystic cavity could be distinguished at this point. No definite inferior margin

Fig. 6 (case 5).—Patient with dermoid of the frontal bone. He had been treated repeatedly by aspiration with inflammation of orbit resulting from leakage into the orbit of the toxic content of the cyst. This cyst had recurred twenty years after supposed complete extirpation.

of the lesion was evident. The orbit showed increased density of soft tissues and increased intraorbital pressure. The impression was that of dermoid cyst, diploic in origin.

Operation (Dr. M. Wheeler).—An incision at the orbital margin above revealed a brownish mass bulging into the orbit; the growth was approximately the size of a golf ball, firm to the touch and fixed in position. An incision released a great quantity of brownish yellow, oily fluid with large masses of glistening material, which obviously was cholesterol. The cyst was cleaned of its content, treated with phenol and alcohol, and as much of the wall as possible was dissected away. The course of healing was uneventful.

Pathologic Report.—Examination revealed an epithelium-lined cyst with cholesterol clefts, fibrous outer wall, hemosiderin, chronic inflammation and products of degeneration. The diagnosis was dermoid cyst involving the orbit.

Comment.—This case would seem to represent a later stage of the same type of lesion, and in a similar position, as that in case 3. In

case 5 the cyst in the roof of the orbit appears to be in an even later stage, also to arise in a similar position. The deep defects in the bone attest the congenital origin of these lesions.

CASE 5.—*Dermoid Cyst, Diploic, of Roof of Orbit, Causing Extreme Degree of Exophthalmos. Huge Defect or Fossa in Roof of Orbit Revealed in Roentgenogram. Recurrence. Preoperative Diagnosis: Dermoid of Orbit. Operation, With Removal of Cyst.*

M. P., aged 63, a white cabinet maker, had had exophthalmos of the left eye, with operation and removal of a cyst from the orbit twenty years before in Germany. Fifteen years later the eye began to bulge again. A large, fluctuant mass could be palpated above, displacing the eye down and outward 11 mm. Both lids were edematous. The patient refused to be hospitalized, and the referring physician requested that the cyst be drained by trocar. A large quantity (18 cc.) of chocolate-colored, oily fluid with small masses of cholesterol was withdrawn and the eye returned to a more normal position. One month later, the patient returned with the eye as prominent as before. Again the cyst was drained, but a considerable reaction followed. The eyelids were tremendously swollen, tender and sore. Several weeks later hospitalization was effected, and the cyst was removed.

The roentgenographic report described a very large cavity in the roof of the orbit, measuring 3 by 5 cm., posterior to the margin with clearcut edges, some increase in bone density in places at the margin and diminished density of the lesion itself. A definite cyst wall could be distinguished bulging into the orbit. The zygomatic process of the frontal bone was thin, atrophic and deformed. The dimensions of the orbit were increased, evidencing a lesion of long duration. There was no communication with the adjacent, normal, frontal sinus.

Operation (Dr. R. L. Pfeiffer).—Through an incision below the brow, a chocolate-colored mass was exposed under a greatly thinned orbital margin, which was removed in part. The fluctuant mass was incised, and the brownish yellow, oily fluid was liberated, with large, cakey, yellowish, glistening masses of cholesterol. No hair was seen. The cavity, large enough to accommodate a golf ball, was cleaned, treated with phenol and alcohol and then dissected out as completely as possible. The wound was closed without drainage, and healing was uneventful.

Pathologic Report.—Examination revealed a fibrous, inflammatory mass with foreign body giant cells, cholesterol crystals and hemosiderin. Epithelium was not found. The diagnosis was cholesteatoma.

Comment.—The severe inflammation which followed the second drainage was probably due to the toxic content of the cyst coming in contact with surrounding tissues at the orbit. Obviously the dermoid cyst cannot be drained successfully . It must be removed carefully and completely.

CASE 6.—*Dermoid, Diploic, Occupying Right Anterior Cranial Fossa, Encroaching on Orbit, to Cause Exophthalmos. Calcified Area in Wall of Growth, Size of Tennis Ball, Revealed in Roentgenogram. Preoperative Diagnosis: Dermoid. Operation, With Partial Removal of Tumor.*

C. M., an 18 year old Negro girl from Jamaica, in good health, complained of increasing prominence of the right eye for the past two years. The eyeball was

displaced down and outward, with exophthalmos measuring 12 mm. A firm mass could be felt above through the upper lid, and prolapse of the lacrimal gland was apparent. Vision in each eye was 20/15 with correction. Diplopia was not bothersome.

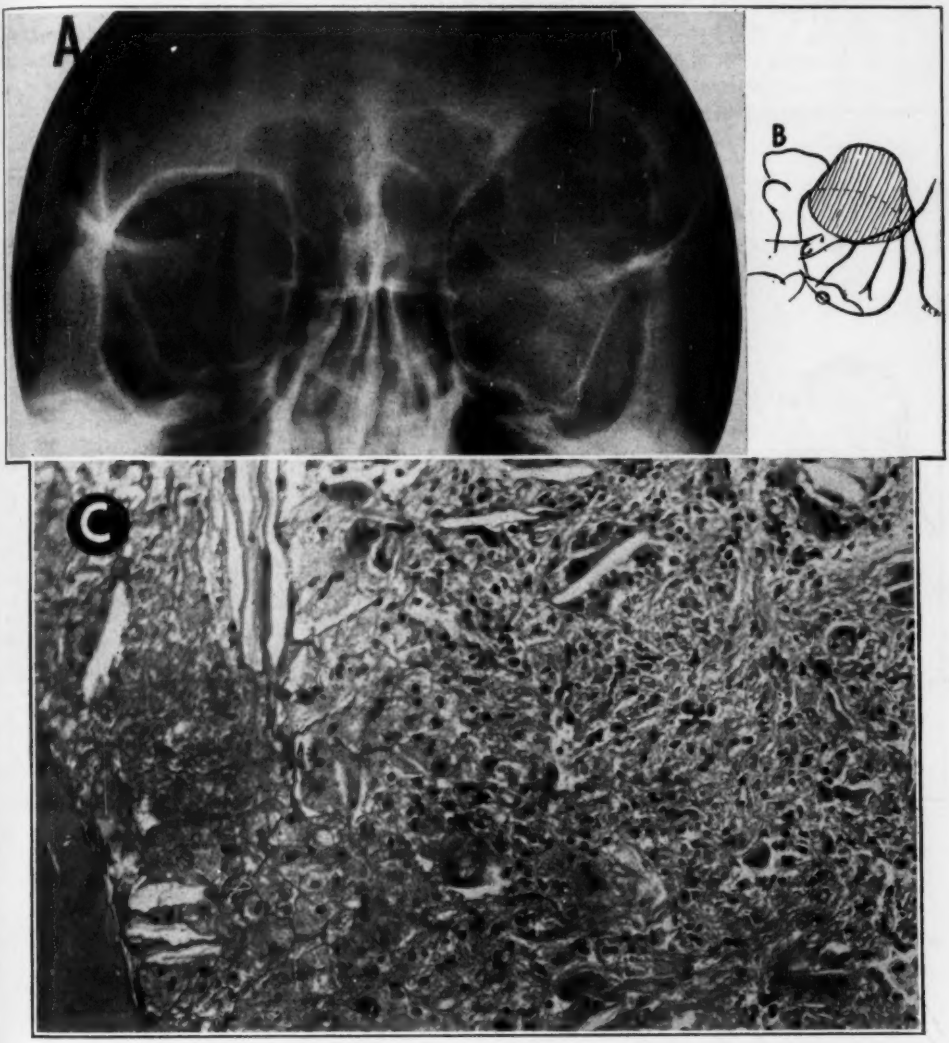

Fig. 7 (case 5).—Large diploic dermoid of the frontal bone deforming the orbit and producing very severe exophthalmos. Note calcium in inferior wall of cyst. *C* (high power section) shows tissue described in text.

Roentgenographic examination disclosed a cystlike, spherical mass the size of a tennis ball in the right frontal fossa and encroaching on the orbit. The wall of the cyst was densely calcified and was complete above and thin below in the orbit, where a thin, linear shadow of calcium extending midway down

into the orbit located its inferior limitation. The roof of the orbit had been completely replaced from the margin in front to the sphenoid ridge posteriorly. The content of the mass showed diminished density. The diagnosis was dermoid cyst of extraordinary proportions arising in the roof of the right orbit or in the frontal fossa and encroaching on the orbit, to produce exophthalmos.

Operation (Dr. J. Scarff of the Neurological Institute).—Through an osteotomy opening in the right frontal area, a large cystic cavity was entered and observed to be filled with a thick, mucilaginous, brownish fluid containing hemosiderin and

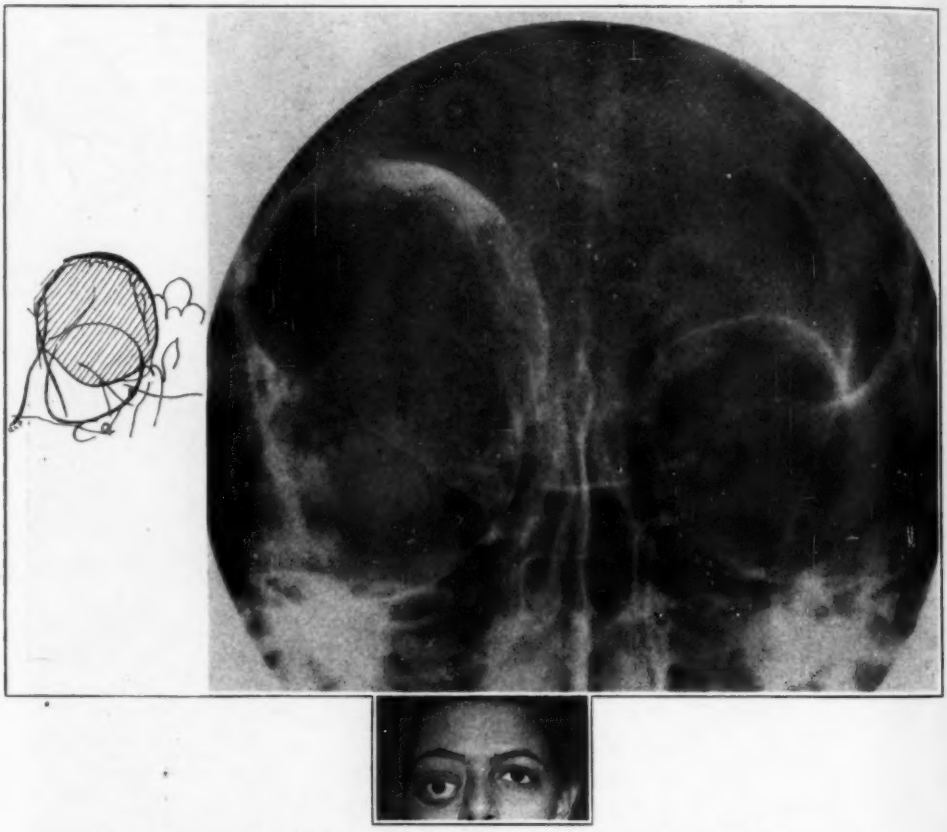

Fig. 8 (case 6).—Diploic dermoid arising in bone of roof of right orbit, reaching startling size, to occupy much of the right frontal fossa and orbit and producing extreme exophthalmos. Calcium can be seen in all parts of the wall of the cyst.

cholesterol. The cyst was drained of content and was found to be multiloculated and lined with stratified squamous epithelium. A mass of solid tissue was found in a recess and was removed. The inferior wall of the cyst in the orbit was excised in part to decompress the orbit and allow the eye to assume a better position.

Pathologic Report.—The specimen consisted of bone invaded by a cystic epithelial tumor. In the hollowed bone a poorly demarcated band of layered

epithelium rested on a thin layer of loose-meshed connective tissue. The epithelial cells in areas were observed to be undergoing degeneration, with clusters of hemosiderin-laden phagocytes among them. Masses of cholesterol were evident.

Comment.—This tremendous cyst, which occupied most of the right frontal fossa and half the right orbit, produced extreme exophthalmos but no profound symptoms. There were no symptoms relating to the central nervous system, and vision in the right eye was normal. The cyst seemed to have arisen in the diploic bone of the roof of the orbit as a congenital epithelial rest to grow in all directions—expanding as a spherical mass to reach startling dimensions.

The excision of the cyst was incomplete, and subsequently several aspirations of as much as 20 cc. of chocolate-colored fluid were performed six weeks after the operation. The area of the excised bone of the right frontal region was distended when last examined, and the position of the eye was unimproved.

CASE 7.—*Dermoid of Left Orbit, Apparently Subperiosteal, Causing Exophthalmos. Mass in Enlarged Orbit Revealed in Roentgenogram. Preoperative Diagnosis: Pseudotumor or Dermoid. Operation: Removal of Large Dermoid.*

R. H., a white man aged 47, gave a history of having had a sinus operation eight years before, without benefit. Six years later the left upper eyelid began to droop, and subsequently the eyeball was displaced from the socket to such a degree that it was impossible for him any longer to close his eye, except with the use of his hand. Double vision developed, but subsequently the vision of the eye failed and he was no longer bothered. No pain or distress was noted. Examination disclosed the right eye to be normal and the left to be displaced outward and downward, with approximately 20 mm. of exophthalmos. A large and very firm mass could be palpated through the upper lid. Vision in the eye was 20/100, and slight papilledema was manifest. There was limitation of motility in all directions, most marked superiorly.

Roentgenographic examination disclosed that the right orbit was normal and the left greatly enlarged in all dimensions, with a mass of increased density above, the tumor thinning and elevating the roof of the orbit anteriorly, where a dihiscence in the bone was apparent. Medially, the mass bulged into the frontal sinus, which cell was otherwise perfectly clear. An oval defect or opening, measuring approximately 0.5 by 2 cm., was present in the lateral wall of the orbit posterior to the temporal line. The margins of the defect were clearcut, and in places increase in the density of the bone could be seen. The density of the tissue in the defect was diminished, in contrast with most of the tissue above. The zygomatic process of the frontal bone was thin and atrophic where the mass impinged on it. The nasal wall of the orbit was concave, and the floor was depressed slightly into the antrum. The optic canals were circular, measured 5.5 mm. in diameter and were symmetric.

Impression.—A large mass, measuring approximately 4.5 by 4 cm., with increased tissue density for the most part, was present in the left orbit, extending upward to produce pressure atrophy and displace the roof anteriorly. An oval defect with diminished density was present in the lateral wall. That the adjacent frontal sinus was clear made it improbable that the lesion arose within it and thus excluded the possibility of mucocele. The defect in the lateral wall was more consistent with the diagnosis of pseudotumor but was suggestive of a congenital lesion, probably a dermoid.

Operation (Dr. R. L. Pfeiffer).—A curvilinear incision was made over the margin of the orbit above down to the periosteum, which was raised to expose a chocolate-colored mass beneath. The margin of the orbit was sharp and thin as a result of pressure. An incision was made into the tumor, and a great quantity of semifluid, dark brown matter resembling thick mud, though with cholesterol crystals evident, was spooned out. The wall of the tumor was firmly adherent above, and a large, smooth, soft and fluctuant area was palpated in the roof of the orbit. This represented the dehiscence seen roentgenographically and was no doubt the dura presenting in it. At several places within the wall of the cyst bleeding developed but was not troublesome. The lining of the cavity was treated with phenol and alcohol and was washed with saline solution. Subsequently, as

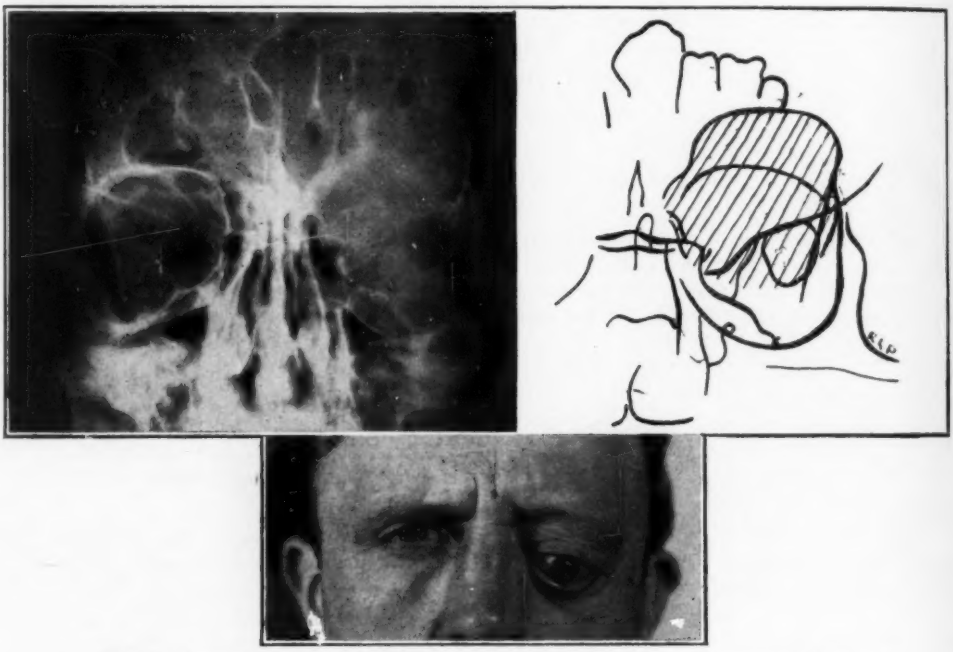

Fig. 9 (case 7).—Subperiorbital dermoid of left orbit with unusual features. The increased soft tissue density of the mass itself is due to the great hemosiderin content. A fossa of diminished density can be seen in the lateral wall, with typical appearance.

much of the wall was removed as was feasible. At operation considerable care should be exercised that the roof of the orbit not be perforated.

Pathologic Report.—In a specimen consisting almost completely of an encapsulated mass of tissue, the bulk of which consisted of spaces containing cholesterol and surrounded by a foreign body cell reaction, many large foreign body giant cells, some containing blood pigment, were observed. The cholesterol spaces were lined with rather flat cells, which did not look like epithelium. Large foam cells, suggesting fat necrosis, were present. Considerable blood pigment, especially in the connective tissue capsule, suggested possible pressure necrosis of fat by hemorrhage. The diagnosis was cholesteatoma.

Follow-up Period.—After the operation the eye returned to a much improved position, with exophthalmos of 2 mm. remaining and displacement of the eye inferiorly 2 or 3 mm. Partial ptosis persisted. Vision in the eye was 20/40 with correction and the fundus was normal. Through a two year follow-up period no change was observed. The patient died subsequently of a heart attack.

Comment.—The roentgenographic findings in this case were confusing. The increased soft tissue density of the main portion of the mass was probably due to the large amount of hemosiderin. Hemorrhage had probably taken place repeatedly within the growth. The

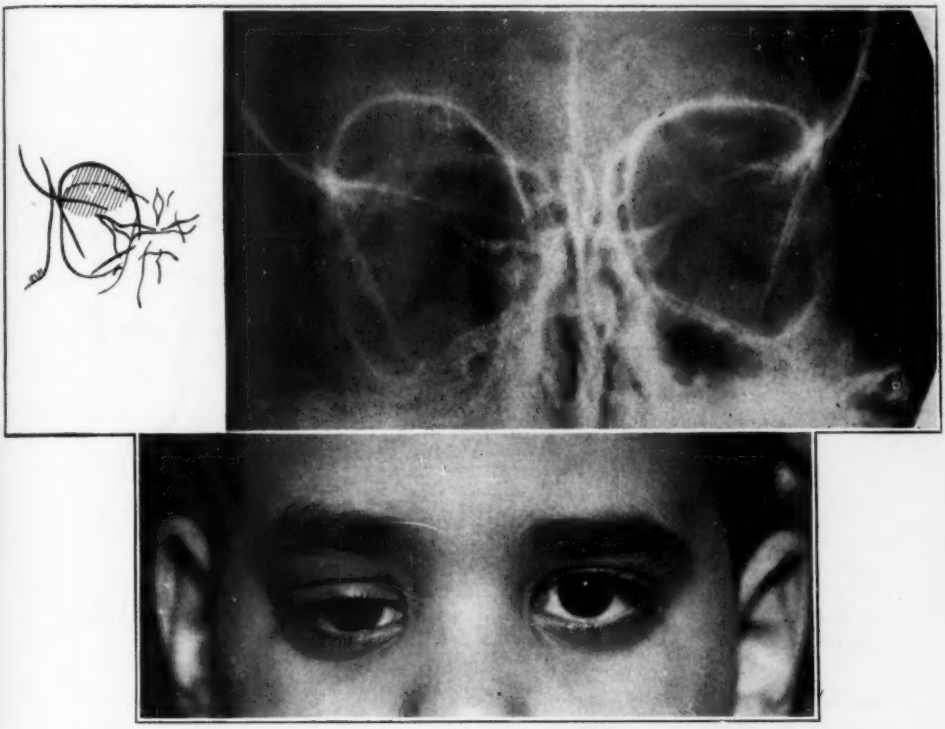

Fig. 10 (case 8).—Dermoid of right orbit perhaps subperiorbital, producing unusual deformity. This is the only growth in which hair was found.

great masses of cholesterol, the fibrous capsule with blood vessels, the absence of communication with the paranasal sinus and the presence of a characteristic defect in the lateral wall of the orbit, all serve to make this an undoubted case of dermoid, probably subperiosteal or diploic in origin.

CASE 8.—*Dermoid of Right Orbit, Producing Exophthalmos and Ptosis. Deformity of Orbit Revealed in Roentgenogram. Preoperative Diagnosis: Hemangioma. Operation, With Removal of Dermoid.*

D. E., a white boy aged 5 years, had been observed to have an abnormality of the right eye since birth, marked chiefly by drooping of the eyelid. Prominence of

right eye had been observed recently. There were no other symptoms or signs. Examination disclosed the right eye to be displaced forward and inferiorly, the exophthalmos measuring 5 mm. Partial ptosis was manifest. Vision of each eye was normal with correction. Except for the weakness of elevation of the eyelids, the extraocular muscles appeared uninvolved. A firm mass could be palpated above the globe and was found to be thoroughly fixed in position. The visual acuity and fundi were normal.

Roentgenographic examination revealed marked asymmetry in the orbits. The left was normal, and the right showed increased capacity with only the vertical dimension increased. The left orbit measured 33 by 40 mm. while the right

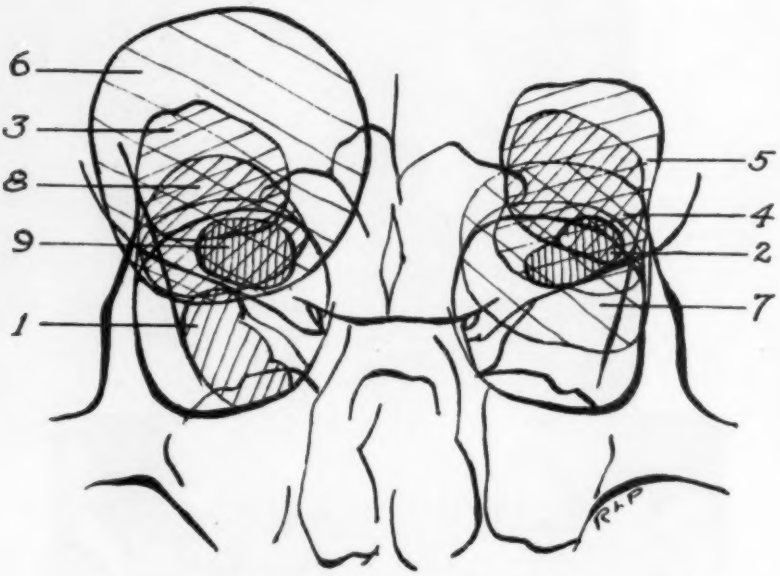

Fig. 11.—Line drawing indicating the locations of the 9 dermoids and their relative sizes.

measured 33 by 50 mm. Thus the deformity of the right orbit was in the upper portion and the roof. The bone of the roof of the orbit was intact throughout, and increased density of the soft tissue was manifest. The sphenoid ridges, sphenoid fissures, temporal lines and optic canals were symmetric. The right antrum was clouded.

Impression.—The extraordinary deformity of the right orbit was undoubtedly congenital and was most suggestive of an hemangioma.

Operation (Dr. J. H. Dunnington).—An incision was made along the upper margin of the right orbit down to the periosteum, which was raised from the bone. The dissection was carried posteriorly over the margin, and a brownish mass was encountered. The exposure was improved, and an incision was made in the tumor. A great deal of cheesy material with hair was liberated. The tumor sac was subsequently dissected out and removed *in toto*. The periosteum

was closed with surgical gut sutures and the cutaneous incision with silk. An intermarginal suture was used to close the eye, after which a pressure dressing was applied.

Pathologic Report.—The specimen was a cyst, the wall of which was missing at one point. The cystic space was lined with keratinized epithelium. In the fibrous wall around this epithelium were rudimentary glands. No hair follicles

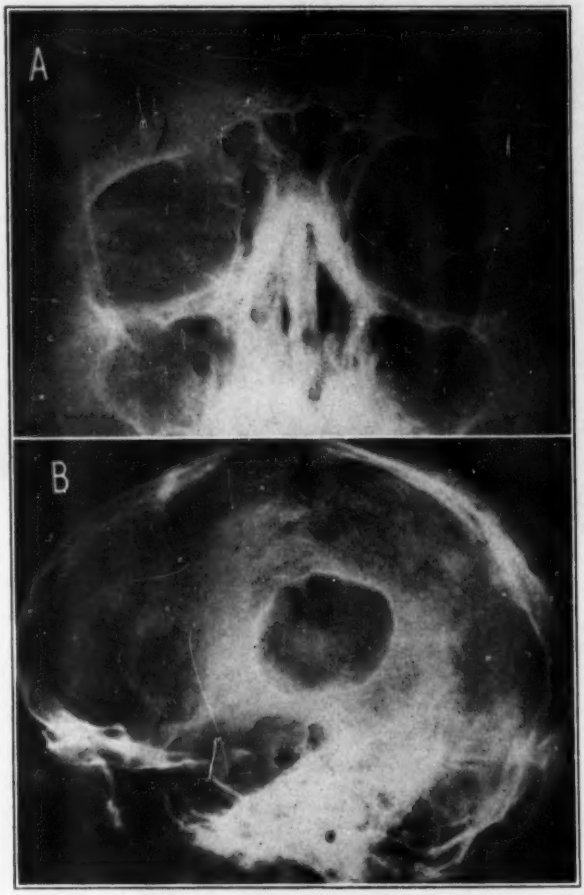

Fig. 12.—*A*, roentgenogram showing dermoid involving the left orbit; *B*, roentgenogram showing a typical dermoid of the vault of the skull.

were seen. There was also rather diffuse lymphocytic infiltration, which in places formed focal accumulations. The diagnosis was dermoid cyst.

Comment.—Hair was found in the cyst at operation but was not reported to be present in the specimen examined in the laboratory. The deformity of the orbit in this case was not typical of dermoid. Its congenital character, however, was apparent.

CASE 9.—*Dermoid, Diploic, of Right Orbit, Causing Exophthalmos. Hiatus in Roof of Orbit Evident in Roentgenogram. Operation, With Removal of Dermoid Cyst.*

S. S., aged 50, a white man with moderately severe diabetes, had observed poor vision in his right eye three years previously. Eighteen months prior to

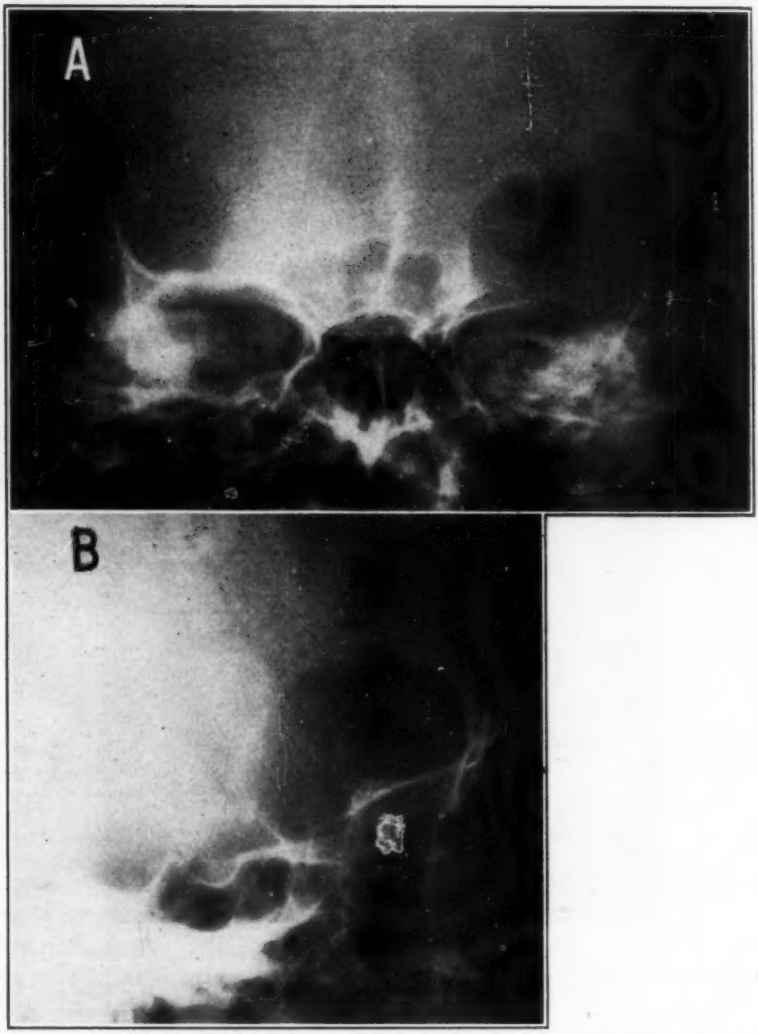

Fig. 13.—Roentgenograms of a dermoid of the left orbit (same patient).

examination double vision developed, and at the same time the eyelids began to droop. Subsequent to this the right eye became prominent, and the prominence had increased. The left eye was normal. Examination disclosed vision of 20/200 in the right eye and 20/30 in the left eye, the latter being entirely normal. The right eye was displaced forward and downward, and exophthalmos measured

9 mm. There was limitation of motility, most pronounced in the field of action of the internal rectus muscle. A mass could be felt above the eye. Ptosis was complete, and the lid could be raised voluntarily. Except for elevation of the blood sugar, the blood chemistry was normal and tests revealed nothing significant.

Roentgenographic examination of the orbits revealed an oval, sharply circumscribed defect, or opening, approximately 2 by 3 cm., in the roof of the right orbit. All the adjacent sinuses were clear, and the sella turcica was normal.

Operation (Dr. John H. Dunnington).—Through an incision in the upper lid of the outer margin of the orbit a large, dark brown, firm mass was revealed attached to the roof of the orbit. The mass was incised, and a large quantity of dark brown, oily fluid with shining crystals and soft masses of mudlike material was evacuated. An opening, measuring 20 by 30 mm., was observed in the roof of the orbit, through which the dura was pulsating. This opening appeared to lie in the middle third of the orbit anteriorly. As much as possible of the wall of the cyst was excised.

Microscopic Examination.—Fragments of tissue removed for study revealed that the cyst wall consisted of dense fibrous tissue with much hemosiderin and clefts containing cholesterol. Spaces lined with epithelium were observed, and in places degenerated fat or foam cells were evident. In other areas the tissue appeared rather necrotic, loose and fibrous, with hemosiderin pigment, and in places areas of fresh blood were seen. Throughout this tissue were abundant cholesterol crystals, surrounded by multinucleated foreign body giant cells. No hair was observed. The diagnosis was cholesteatoma of the orbit, probably of diploic origin.

Comment.—This patient was followed in the clinic for fifteen years, without any evidence of recurrence of the cyst, although not all the cyst wall had been excised and phenolization was not employed.

TREATMENT

Since dermoids of the orbit vary in size, position and composition and may involve neighboring structures and cavities, their treatment requires thorough study of the case and careful planning.[26] Deformity of the orbit is the rule, and proper roentgenographic examination is essential for diagnosis; in addition, the plan of treatment rests on the defect revealed. If a haitus is found in the roof of the orbit, the frontal fossa may be involved, and thus the service of a neurosurgeon may be needed, as in cases 2 and 6. In all cases it rests with the roentgenologist to decide whether or not the defect extends through the bone and possibly involves the adjacent cavity.

In 6 of the 9 cases, direct approach through incision at the margin of the orbit over the presenting masses was adequate. In these cases the periorbita was raised and the bone was followed back to the lesion, which was incised and evacuated. The remaining sac was then phenolized, next treated with alcohol and then irrigated with saline solution. The cyst wall was then removed as completely as possible. The wound

26. Gifford, H.: Treatment of Dermoid Cysts of Orbit, Arch. Ophth. **52**:448 (Sept.) 1923; Recurrent Dermoids, ibid. **2**:305 (Sept.) 1929.

was finally closed tightly in layers, and a pressure dressing was applied, to remain for several days.

Obviously, temporization is not justified. Because of the toxic character of the content of the cyst, aspiration not only will fail to improve matters but also may produce intractable inflammation in the orbit.

SUMMARY AND CONCLUSION

In this paper we suggest the incidence of dermoids and epidermoids, differentiate the one from the other and endeavor to clarify the terminology. Because there is little embryologic and histologic distinction between these growths, it is contended that the name "dermoid" is sufficient to cover both. Intermediate or transitional types are common, and the assumption of a purely arbitrary condition, such as the presence or absence of hair, to differentiate them is not applicable or practical.

All the 9 dermoids involving the orbit and causing exophthalmos reported here were cystic, with epithelial linings which varied greatly in number of layers and appearance of cells and with the content of the cavities consisting of fluid and semisolid matter. The fluid was oily, brown or chocolate in color, due to hemosiderin, and served as a solvent for cholesterol. The semisolid matter consisted of cholesterol and epithelial products. Hair was found in only 1 case.

This series of cases is presented primarily to call attention to defects in the bone which they produce, which may be well studied by roentgenography, and which serve to distinguish these lesions from other causes of proptosis. The characteristic roentgenographic appearance of such a lesion of the bone is that of an area of diminished density with smooth, regular margins of increased density of the bone.

Caution on treatment, whether by neurosurgeon or ophthalmic surgeon, which is determined by roentgenography, is duly stressed. The proper use of phenolization is mentioned.

A SIMPLE OPERATION FOR ENTROPION

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IT IS the purpose of this report to review the mechanism of so-called spastic entropion of the lower lid and to call attention to a simple and effective operation for this condition. This procedure is directed toward correction of the abnormal anatomic relations which predispose to malfunction of the orbicularis oculi muscle.

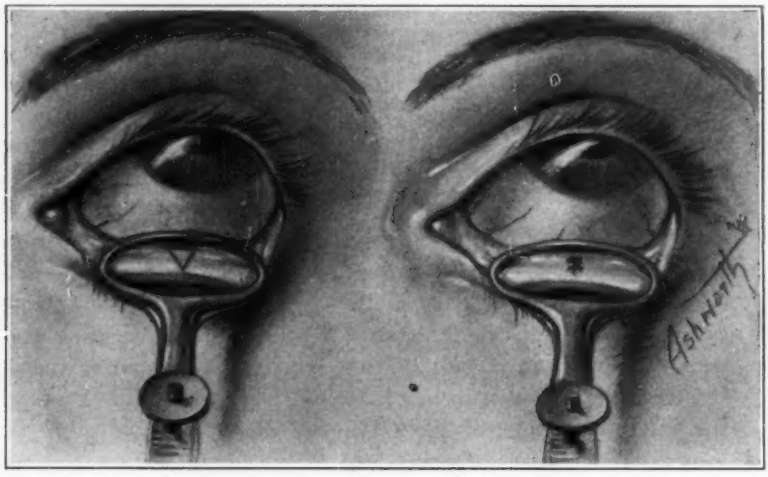
Many operations have been described for the correction of spastic entropion, but none is directed at correction of what seems to be the fundamental cause, namely, an abnormal relation of the tarsal plate to the globe, with resultant improper function of the orbicularis oculi. In some previously described procedures attempts have been made to modify the action of the orbicularis on the tarsus or to buckle the tarsal plate outward either by establishing an everting cicatrix or removing a wedge from the outer surface of the plate parallel to the lid. Other procedures have been directed toward tacking the lower border of the tarsus to the periosteum of the bones of the face either by sutures or by transplanting a strip of orbicularis. Even resections of the skin have been advocated to prevent the lower tarsal margin from everting by tightening the skin of the lids. Only Graefe seems to have considered removal of a wedge from the inferior margin of the tarsus to change its curvature, and then only as a supplemental procedure to his operation for cicatricial entropion.

The tarsal plate is the "skeleton" of the lid and is of the utmost importance not only in maintaining its shape and function but also in directing the action of the orbicularis muscle. In effect, the tarsus is a curved flap of relatively nonelastic connective tissue suspended by tarsal ligaments at its upper outer margin. The lower border is attached to the orbital septum and to an expansion of the fascial sheath of the inferior rectus muscle. In this lies the inferior palpebral (involuntary) muscle. These attachments are relatively loose.

Normally the tarsal plate has a double posterior concavity, which allows it to conform to the shape of the globe. This rather marked anteroposterior concavity of the plate is maintained even in closure of the lids because the lateral palpebral ligaments are attached within

From the Department of Ophthalmology, University of Oregon Medical School.

the orbit well behind the limbus and the tarsus is molded on the eyeball. In normal lid closure the orbicularis elevates the lid margin, stretches the skin smoothly over the lower lid and applies direct pressure to the tarsal plate, thus maintaining its normal snug relation to the globe. In this case the tarsus slides smoothly over its bed, without abnormal rotations occurring. If, however, there has been absorption of orbital and suborbicularis fat, with relaxation of the inferior ligaments, the normal relations of the muscle, tarsus and globe are no longer maintained. Contraction of the orbicularis now straightens the lid margin and tends to force it down, thus relaxing the inferior ligaments. A straight axis is now provided by the shortened and straightened upper border around which the tarsus may rotate in a flaplike manner. In entropion the lack of support by the globe and the relaxation of the inferior ligaments allow



Area of tarsectomy and line of closure.

the lower border of the tarsus to rotate outward around this axis, with the resulting inversion of the upper border. The rubbing of the cilia against the globe stimulates blepharospasm, which tends to exaggerate the condition.

In spastic entropion the normal curvature of the tarsal plate is lost and the inferior border no longer fits the globe snugly, owing to varied changes in elasticity of the tissues and absorption of suborbicularis and orbital fat. In effect, the lower tarsus has become relatively too long and too flat. To correct this and to restore the normal snug relationship of the tarsus to the globe, an inverted wedge is excised from its inferior margin of the tarsus to shorten and, thereby, to increase the curvature of the lower part without disturbing the ligamentous attachments or the orbicularis muscle.

The operation can be performed in a minor surgery room with the use of local anesthesia. With the lid everted on a chalazion clamp, and the conjunctiva prepared for operation, a small incision is made in the conjunctiva and the inferior tarsal ligaments along the lower border of the tarsal plate, usually in the center. The length of incision is usually 3 mm., but the amount of tissue to be removed is a matter of surgical judgment in each case. Small, blunt-tipped scissors are introduced through this opening to separate the tarsal plate from the orbicularis muscle in the region of the expected tarsectomy. In freeing the muscle from the plate, blunt dissection is used to avoid damage to the muscle fibers. This dissection is carried to the follicles of the cilia. Then a wedge of tarsus and conjunctiva is removed (figure). The base is the inferior border of the tarsal plate. The apex is carried almost to, but does not include, the palpebral margin. Little bleeding is encountered, as the vascular supply to the muscle has not been disturbed. In adults, fine interrupted black silk sutures are placed through the conjunctiva and the tarsal plate. In children, surgical gut is used. The knots are placed as low as possible to prevent contact with the cornea. A dressing is used for twenty-four hours, and the sutures are removed in ten to fourteen days.

The period covered in this preliminary work is not sufficient to determine the long range results of the operation, but it seems to be based on sound physiologic and anatomic principles. The operation is so simple that it can be performed in the office. It has the further advantage of producing no external scarring because the approach is from inside the lid. Also, this operation does not interfere with other lid procedures, as do the commonly performed Ziegler punctures or other cicatrizing operations. It has been so successful in the University of Oregon medical clinics that it merits a trial by various surgeons, with a diversity of cases, to determine whether it stands the test of time.

PRACTICAL APPLICATION OF SURFACE-ACTIVE DRUGS IN OPHTHALMOLOGY

J. B. FELDMAN, M.D.

P. DeLONG M.D.

AND

C. P. BROWN, M.D.

PHILADELPHIA

WETTING AGENTS

WITHIN the last twenty odd years there have been produced a number of synthetic chemicals analogous to soaps. These agents, like soaps, penetrate the "supposed tension of the surface" of any liquid but, unlike soaps, are not affected by hard water. The name "surface-active agents" has been given to these synthetic preparations.

The "Glossary of Physics" [1] gives this definition of surface tension:

> . . . the peculiar effect of cohesion manifested at the free surface of a liquid or at the interface of two immiscible liquids, and giving the impression of a tense elastic skin membrane. It is measured in units of force per unit length, e. g., dynes per centimeter along the line on the surface.

A number of these surface-active agents have been prepared [2] to be used in such diverse industries as the manufacture of shampoos, dentifrices, inks, dyeing products, cosmetics, lubricating materials, the processing of leather, textile industries, air conditioning and fruit and vegetable peeling.

It is not necessary to mention that a great number of these products are much too acrid for use in ophthalmology. Many manufacturers are aware of this and warn against the promiscuous use of these products in medicine.

Johnson [3] and others have called attention to the fact that surface activity is not completely understood and that the phenomena of detergence in all its phases have not as yet been analyzed. However, a number of the surface-active agents have been checked on animals to determine any ill effect, thus: Hatton [4] fed irium, a sodium lauryl sulfate preparation with a small percentage of sulfated alcohols, in

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1. Weld, L. D.: Glossary of Physics, New York, McGraw-Hill Book Company, 1937.

2. Young, C. B. F., and Coons, K. N.: Surface Active Agents, Easton, Pa., The Chemical Publishing Co., Inc., 1945, pp. 117-154.

3. Johnson, H. C. E.: Scient. Am. **174**:57, 1946.

4. Hatton, E. H., and others: J. Dent. Research **19**:87, 1940.

massive doses to rats without any untoward results. Gershenfeld and Wittin [5] gave massive doses of surface-active agents to rabbits intravenously and intraperitoneally for several months without any disaster. Several preparations have been used in dermatology.[6] Roth [7] suggested their use in ophthalmology.

Bellows and Chinn, [8] in experiments on animals, found a low percentage of chemotherapeutic agents in the aqueous after oral administration of the drugs. They stated the belief [9] that these sulfonamide drugs are better absorbed directly through the cornea. In later experiments on rabbits using chemotherapeutic drugs to the cornea with no wetting agents, satisfactory results were obtained.[10] At that time these observers suggested the use of these surface-active drugs in combination with mydriatics, miotics and antiseptics.

Theoretically, at least, surface-active agents should be ideal as vehicles for ocular medication, and with that thought in mind it was decided to check the foregoing data on human subjects.

BACTERIOLOGIC TESTS [11]

To assure ourselves that no deleterious effect would result from the use of any of these agents in our patients, it was decided first to recheck the animal experiments of surface-active drugs on rabbit eyes. A number of surface-active drugs were made up in 1 per cent solutions. Ringer's solution was used to make them isotonic. They were buffered to p_H 7.3,[12] put up in 8 ounce (236 cc.) bottles, capped and left undisturbed for six months. They were then checked for sterility by inoculating 50 cc. volumes of culture mediums in fermentation tubes with 10 drops of each solution. The tubes were incubated for ninety-six hours at 37 C. Of the eleven solutions tested, triton X30® (sodium salt of aryl alksyl ether sulfate) and tween 80® (polyoxyalkylene ether

5. Gershenfeld, L., and Wittin, B.: Am. J. Pharm. **113**:215, 1941.

6. Duemling, W. W.: Wetting Agents: New Synthetic Chemicals, Arch. Dermat. & Syph. **43**:364 (Feb.) 1941. Goodman, H.: Cosmetic Dermatology: Triethanolamine, ibid. **36**:116 (July) 1937. Maynard, M. T. R.: Triethanolamine: Adjunct to Dermatologic Therapy, ibid. **25**:104 (June) 1932; ibid. **34**:268 (Aug.) 1936.

7. Roth, R. J.: Am. J. Ophth. **29**:717, 1946.

8. (*a*) Bellows, J. G., and Chinn, R.: Arch. Ophth. **25**:294 (Feb.) 1941.

9. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34 (Jan.) 1942.

10. Bellows, J. G., and Gutmann, M.: Application of Wetting Agents in Ophthalmology, with Particular Reference to Sulfonamide Compounds, Arch. Ophth. **30**:352 (Sept.) 1943.

11. Mr. F. Wilson did the bacteriologic studies.

12. Feldman, J. B.: p_H and Buffers in Relation to Ophthalmology, Arch. Ophth. **17**:797 (May) 1937.

of partial oleic acid ester) were unsterile. Subcultures of blood agar plates revealed identical gram-negative bacilli in these two solutions. Saline suspensions of these organisms failed to produce any deleterious effect when introduced into the eye of a rabbit.

In the second batch of the same agents set up and examined in several days, the sterility tests, curiously, showed the same results as in the test cited above; i. e., triton X30® and tween 80® were again unsterile. From this observation, one would assume that the gram-negative bacilli must have been in the parent surface-active drugs, since the same parent wetting agents were used in making these identical dilutions six months apart.[13]

ANIMAL EXPERIMENTS

The animal experiments consisted in first instilling 3 drops of each solution into the eye of a rabbit, using a sterile pipet. The eye was observed at the time of instillation and at half-hour intervals over a period of three hours and on the following morning. On the following day the animals received two doses. The second dose was given three hours after the first. Unless it is mentioned, the same solution was used for the same eye of the rabbit throughout the study. Triton X135® and ultra-wet 30 DS® (an alkylated monosodium benzene sulfate) gave no apparent reaction at any time. These were therefore best tolerated; they comprised group 1. Group 2 consisted of triton X30® and tween 80®, which were not as well tolerated as the drugs in group 1. The rabbit eyes tested in this group consistently showed slight capillary congestion within two minutes after triton X30® and within five minutes after tween 80® was dropped into the eye. Nacconol N R S F® (sodium allyl aryl sulfonate) and ultra-wet E® gave even more congestion but, not appearing to be destructive to the corneal epithelium, were included in the second group.

The surface-active drugs which caused variable degrees of capillary congestion, chemosis, mucoid discharge and terminate edema were in the last group. In 1 case the pain caused the animal to squeal for a full minute after the instillation. These drugs comprised group 3 and included duponol C® (an alkyl sulfate), santomerse D® (an alkylated aryl sulfonate), tergitol penetrant 7 (a higher secondary alcohol sulfonate), C T A B® (cetyl trimethyl ammonium bromide) and aerosol O T (dioctyl ester of sodium sulfosuccinic acid).

For obvious reasons, group 3 was omitted from our clinical study on patients.[14] It is known that the rabbit eye is more sensitive than the human eye.

CLINICAL EXPERIMENTS

Dosage.—One of the purposes of using surface-action agents is that, since they are good wetting agents and should penetrate the cornea rapidly, only a minimal dose need be employed. The concentration of these ophthalmic drugs

13. It was later decided that when these surface-active drugs were tolerated by the eye it was not necessary to alter their p_H or to make them isotonic.

14. Some of the solutions of surface-active agents were clear; others, slightly turbid; a few, even cloudy. No attempt was made to filter these solutions. It was found that the turbid solutions were slightly more painful than the clear ones but acted more effectively.

tested, therefore, was placed arbitrarily at 0.5 per cent, to be adjusted later as deemed necessary. Solutions of surface tension agents with atropine sulfate, paredrine hydrobromide ophthalmic® (1 per cent solution of *p*-hydroxy-*a*-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved with merthiolate,® 1 : 50,000), pilocarpine hydrochloride, eucatropine hydrochloride, tetracaine hydrochloride, nitromersol N. F. (metaphen®) and homatropine hydrobromide were made.

Records.—The patient's name, age, color of iris and diagnosis were recorded, as well as the medication used, the intervals of instillation and the reactions obtained. When a mydriatic was used, an attempt was made to obtain the reaction to light, as well as to check the cycloplegic effect of the drug. The latter was affected by adding a + 3 sphere to the refraction and by having the patient read .37 M type through a 3 mm. opening. Measurements were made with the Prince rule. This was done only with intelligent patients, when it was felt that rapid and trustworthy cooperation could be obtained. A number of patients were tested at the same period by the same combination of drug and surface-active agent, in order to determine whether or not the same therapeutic and beneficial effect was consistently obtained.

Finally, when a mydriatic was used, we recorded how long it took the pupil to return to normal with and without pilocarpine. It had been observed with previous mydriatics that the "blue iris" dilated fastest; the result was the same with our surface-active mediums. The color of the iris did not affect the burning or stinging after instillation of a surface-active agent.

Examination of Patients.—There remained, then, after the experiments with rabbit eyes, two groups of surface-active agents to be used on our patients. Group 1 included the preferred surface-active agents, triton X155® and ultra-wet 30 DS.® Group 2 included the agents to be used with some caution: triton X30,® tween 80® and particularly nacconol N R S F® (polyoxyalkylene ether of sorbitan and ultra-wet E® mono-oleate).

All surface-active agents bore a number unknown to us so that an unprejudiced opinion could be expressed when a preparation was used. Sometimes the same wetting agent was used on both eyes. Often the same drug in different wetting agents was used in the eyes of the same patient to determine the relative effectiveness of each surface-acting drug. Occasionally the same drug in many surface-active agents was used in the same eye in order to observe the cumulative effect of both the wetting agent and the ophthalmic drug.

Before any ophthalmic drugs were used, 50 patients were tried out with the surface-active agents of group 1 only. Having found no ill effect from the use of the wetting agents of this group, we tried paredrine and pilocarpine in combination with wetting agents of groups 1 and 2 in a series of 100 patients. After we found that the ophthalmic drugs were tolerated with surface-active agents, there were prepared solutions of 1 per cent surface-active agents with 0.5 pilocarpine hydrochloride, paredrine hydrobromide ophthalmic,® tetracaine (pontocaine®) hydrochloride, eucatropine (euphthalmine®) hydrochloride atropine sulfate, and homatropine hydrobromide, 0.5 and 1 per cent.

As before mentioned, the labels contained the name of the ophthalmic drug and a number only, signifying the wetting agent. With the patient's head tilted back, and with him looking down, single drops were instilled at the upper margin of the limbus. When a mydriatic was used, the patient was usually in a darkened room.

OPHTHALMIC DRUGS

Paredrine Hydrobromide Ophthalmic.—Two hundred and fifty-one patients with ophthalmic disorders were examined (table 1). A large number obtained full dilation. Only 2 of these gave no reaction to light; all could read even though there was a maximum dilation, and none gave evidence of cycloplegia. The average time of full dilation was from thirty to eighty-seven minutes. One Negro woman,[15] aged 34, obtained full dilation with two instillations in eighty minutes. Another woman, white, aged 66, with hazel eyes and optic nerve atrophy, obtained full dilation, with ultra-wet 30 DS® for the right eye and ultra-wet E® for the left eye, in forty minutes. On the other hand, in about a dozen cases the pupil did not dilate to more than 6 mm. even though four or five instillations of the drug were given, up to seventy minutes in some cases.

TABLE 1.—*Use of Ophthalmic Drugs in Wetting Agents*

Ophthalmic Drugs, 0.5%	"Triton × 155"	"Ultra-Wet 30DS"	"Ultra-Wet E"	"Nacconol NRSF"	"Triton × 30"	"Tween 80"
Paredrine hydrobromide	57	55	32	28	38	41
Pilocarpine hydrochloride	47	26	16	20	15	8
Tetracaine hydrochloride	19	23	7	..	..	..
Eucatropine hydrochloride	4	4	8	3	2	9
Homatropine hydrobromide, 0.5 %	33	37	..	..	1	..
Homatropine hydrobromide, 1%	23	23	..	..	..	..
Atropine sulfate	15	14	14	2	10	10
Aqueous nitromersol	3	4	..	..	..	..

Of the various surface-active agents used, ultra-wet 30 DS® and ultra-wet E® gave a stinging sensation, and nacconol NRSF burned a great deal in a few cases. In some cases the first instillation burned but the succeeding drops did not.

To determine the relative merits of ultra-wet E® and tween 80® with 0.5 per cent paredrine hydrobromide ophthalmic,® we instilled the drops in the eyes of a large number of patients. It was found that ultra-wet E® gave the more severe pain. In fact, one elderly person had a mucoid discharge with a sensation of a foreign body for several days. Another elderly woman had chemosis with some edema; this woman had photophobia and a sensation of a foreign body for about three weeks.

In a woman aged 23 with hazel eyes, 0.5 per cent paredrine hydrobromide ophthalmic® in triton X30 was used for the right eye, and the same mydriatic in triton X155,® for the left eye. Four drops were instilled over a period of forty-five minutes, resulting in a 5 mm. pupil in the right eye and a 4 mm. pupil in the left eye. It is interesting that in

15. In Negroes, mydriatics of much higher potency are required to obtain full dilation.

this case triton X155,® which was previously known to be the least painful agent, was rather painful. Usually when the surface-active agents did produce pain, the physiologic effect of the associated ophthalmic drug was rapid. In this case, however, dilation was poor in the right eye. In the left eye, the entire epithelial layer of the cornea was denuded within forty minutes. There was photophobia, but not severe pain, with such blurred vision that none of the letters on the Snellen chart could be read. In several hours the epithelial layer of the cornea was reformed, but slight pain and photophobia prevented the patient from seeing the 6/60 line on the chart. The next morning she had 6/6 vision in each eye.

Not all patients had the same degree of corneal sensitivity. A woman of 25, with hazel eyes, received 0.5 per cent paredrine hydrobromide ophthalmic® in the right eye with the following surface-active agents: tween 80,® ultra-wet E,® nacconol NRSF® and, lastly, triton X30.® In the left eye there were instilled 0.5 per cent paredrine hydrobromide ophthalmic® in nacconol NRSF,® triton X30® (on three occasions) and, lastly, nacconol NRSF.® The drops were given over a period of eighty minutes. Except for a slight burning for five minutes after the first instillation of nacconol NRSF® to the left eye, there were no ill effects. There was full dilation of the pupil, but the eye still reacted to light and there was no cycloplegia.

Examination of a number of patients for tolerance and the mydriatic effect of paredrine proved that the surface-active agents were of value in the following order: triton X30,® ultra-wet 30 DS,® triton X155,® tween 80® and, lastly, ultra-wet E.®

Pilocarpine Hydrochloride.—The number of patients examined was 132. In most cases in which nacconol NRSF® was used the burning was severe and lasted for a considerable period. Very little pain was experienced with triton X30® and ultra-wet E.® No pain was felt with tween 80,® triton X155® or ultra-wet 30 DS®; yet when pilocarpine was given to patients for home use, the pain was so severe that the drug had to be stopped. This happened to 4 patients with refractory simple glaucoma. On the other hand, of an equal number of patients who were operated on for glaucoma (basal iridectomy), 3 had been using the same combination of 0.5 per cent pilocarpine hydrochloride to an ounce (30 cc.) of triton X155® for three months with no ill effects. Only 1 of these patients had to discontinue the medicine because of the severe pain experienced.

Tetracaine Hydrochloride.—Clinically, we observed that with 2 exceptions, tetracaine in a solution of a surface-active agent, gave pleasant, rapid and unquestionable anesthesia. This effect was explained

by Swan and White [16] as due to the pronounced lowering of surface tension by the tetracaine. In the 40 subjects tested, with the 2 exceptions to be noted, it did not make any difference which of our surface-active drugs was used.

Good anesthesia was obtained with triton X30® and ultra-wet 30 DS.® In a case in which tetracaine was used in nacconol NRSF,® the patient said, "For a while there was a sensation of a foreign body in the eye." In a second case, that of a young woman, an instillation of tetracaine in triton X155® produced a heavy mucoid discharge with much burning, the latter improving only after numerous irrigations of boric acid solution.

On the other hand, some patients were given tetracaine in a number of wetting agents to the same eye with no ill effects; for example, a patient received three instillations of several drops of tetracaine in triton X155,® ultra-wet 30 DS® and ultra-wet E® in each eye over a period of an hour, with no untoward symptoms.

Eucatropine Hydrochloride.—This drug was tested on 30 patients. All received from two to six instillations over a period of forty to seventy-seven minutes. The ages of the patients varied from 33 to 72 years. The pupils dilated from 5 mm. to a maximum of 7 mm. In 1 subject, an 8 mm. pupil was obtained. All the pupils reacted to light, and all the patients could read with maximum dilation.

Homatropine Hydrobromine, 0.5 Per Cent.—Seventy-one patients were studied. Full dilation was obtained in from thirty to ninety minutes. An exception was a 10 year old girl with brown eyes for whom eighty-five minutes was required for dilation to only 3 mm. in the right eye and to 4 mm. in the left eye.[17] Some patients obtained definite cycloplegia. In most patients the pupil did not react to light. In a few cases from two to five instillations were necessary to obtain full mydriasis.

After this study, 23 unselected subjects received 1 per cent homatropine hydrobromide in triton X155® in one eye and the same mydriatic in ultra-wet 30 DS® in the other eye, for comparative studies. It was found that homatropine hydrobromide in ultra-wet 30 DS® worked more efficiently. This finding applied to the 0.5 as well as to the 1 per cent solution.

Full mydriasis was obtained in thirty to eighty minutes with one or two instillations. Seven patients with fully dilated pupils had no cycloplegia and could read. Sixteen patients evinced definite cycloplegia. Two patients with 7 mm. pupils did not react to light and were

16. Swan, K. C., and White, N. G.: Am. J. Ophth. **25**:1043, 1943.

17. It is possible that this poor mydriasis was due to the mydriatic's being flicked out because of pain caused by the wetting agent.

instructed to return later. In two hours the pupils were fully dilated, and, as previously noted, there was no reaction to light. They could not read, and they had definite cycloplegia. In some cases the pupils were dilated for twenty-four to thirty-six hours.

Atropine Sulfate.—Sixty-five patients obtained full mydriasis in from twenty-five to, in 1 case, eighty minutes. For the majority one hour was required. Two patients for whom nacconol NRSF® and triton X30® were used experienced a slight "scratching sensation." Because the children were very young, cycloplegia was not tested. An older child with a fully dilated pupil could make out the .37 M type. With several patients atropine was used in a surface-active agent for a week with no ill effect.[18] The dilation lasted about seven days in the majority of cases.

Aqueous Nitromersol (Metaphen®).—Aqueous nitromersol (1:5,000) in triton X155® and ultra-wet 30 DS® was used in 7 cases. The pain was intense in each case. An effort to dilute the solution to 1:10,000, and even to 1:15,000, yielded no better results. On the other hand, a woman aged 70 with chronic dacryocystitis could not use a 1:10,000 solution and was advised to continue with the drug in spite of the pain. She persisted, and her eye improved. Of course, it might be that her condition would have improved, chronic conditions having periods of recession.

A dog's eye is the nearest approach to the human eye, the thickness of the dog's cornea being equal to that of the human. We were fortunate in securing a dog who had purulent conjunctivitis. A 1:10,000 aqueous solution of nitromersol was used alternately in triton X155® and ultra-wet 30 DS.® Both solutions pained a great deal and gave intense chemosis and edema of the lids. The solutions were stopped, and aqueous nitromersol (1:5,000) without a wetting agent was instilled, with complete recovery of this condition.

About the time our previous studies were completed, we were fortunate in obtaining several wetting agents not procurable previously. Among these were tween 80® and triethanolamine, U. S. P., both the commercial and the purer type,[19] sent directly to us by the manufacturer. The other wetting agents were hyamine L4-669,[20] a local antiseptic similar to benzolkonium chloride (zephiran chloride®), and several varieties of the tritons, varying in p_H from 8 to 9.

18. A number of these patients were from ophthalmic clinic at St. Christopher's Hospital for Children, Philadelphia.

19. The purer type is supposed to have less monoethylamine and diethylamine. We found the two types equally useful for our purposes.

20. J. L. Rainey, Ph.D., and L. H. Bock, Ph.D., of Rohm & Haas Company, Philadelphia, suggested the tests with these drugs.

Previously it was learned that a bland surface-active agent may become acrid after the ophthalmic drug is added. To guard against this difficulty, the surface-active agents were checked in a 1 per cent solution on rabbit eyes and, in addition, were rechecked with the 0.5 per cent solution of the ophthalmic drug added to the wetting agent. Included in this study also were some ophthalmic drugs not previously used with ultra-wet 30 DS® or triton X155.® Also used were decresol OT (dioctyl ester of sodium sulfosuccinic acid), tergitol 4 and nacconol L.A.L.

ANIMAL STUDIES

Method of Procedure.—Three drops of the ophthalmic drug with the surface-active drug was instilled in the eye of a rabbit twice daily for two days. Observations were made at the time of administration and at one hour intervals during the day. A different eye was used for each medicament.

As a result of these studies, it was found undesirable to use fluorescein, mild protein silver, sulfathiazole and sulfadiazine in ultra-wet 30 DS,® but they were tolerated when used in triton X155.® We found that decresol OT,® tergitol 4® and nacconol L.A.L. were undesirable. We also discarded (1) paredrine in tween 80® (table 2); (2) pilocarpine in triton X200®; (3) homatropine dissolved in triton X500,® tween 80,® triethanolamine and triton X200® (table 2) and, (4) atropine dissolved in triton X500 and triton X720 (sodium salt of aryl alkyl polyether sulfonate). The rabbit eye showed no capillary congestion when these same ophthalmic drugs were dissolved in the other of this group of surface-active agents or when the antiseptic hyamine® L4-669 (1:10,000) was used.

LABORATORY STUDIES

EXPERIMENT 1.—At the time, it was thought desirable to observe what effect sulfathiazole would have on the aqueous concentration. Thus, two solutions were made up: one of 3 per cent sulfathiazole in triton X155® and another of 3 per cent sulfathiazole in water, as a control. Twenty-four doses of each solution were instilled in hourly doses during the day for a period of three days. Three drops was used in each instillation. After this period the aqueous fluid was removed from each anterior chamber, and a few hours later the secondary aqueous fluid was removed. Neither fluid contained sulfathiazole. It should be remembered that only triton X155® was used.

EXPERIMENT 2.—A dilution of hyamine L4-669 (1:10,000) was used with the test organism Staphylococcus aureus, FDA strain, in an agar cup plate. Six drops of incubation revealed a zone of inhibition of 3 mm. A portion of the agar in the clear zone was removed and

subcultured in broth. No growth was obtained after forty-eight hours of incubation, an indication that the action of the sample was germicidal. The phenol coefficient of the preparation is Eberthella typhosa 300; Staph. aureus 600. We dispensed this preparation to 20 patients, with good results in cases of catarrhal conjunctivitis and dacryocystitis.

CLINICAL STUDIES

Fluorescein, 0.5 per cent, in triton X155® was used on a number of patients; there was no pain, and the corneal abrasion showed up clearly.

Paredrine Hydrobromide, 0.5 per cent, in Surface-Active Drugs.—In 109 patients full dilation was obtained in from twenty-two minutes to two hours. Some patients did not have more than a 5 mm. pupillary opening. Some had no reaction to light, but many could read with full dilation. None had cycloplegia.

TABLE 2.—*Further Study on Use of Ophthalmic Drugs in Wetting Agents.*

0.5% Solution	"Triton* × 500"	"Triton × 155"	"Tween 80"	"Triton A20"	Triethanolamine	"Triton × 200"	"Triton 720"
Paredrine hydrobromide ophthalmic"	15†	20	9† ‡	18	18	5†	24
Pilocarpine hydrochloride	22	33	28†	20	27	4† ‡	4
Eucatropine hydrochloride	4	5	5†	6	5	7†	6
Homatropine hydrobromide	‡	7	† ‡	9	‡	‡	12
Atropine sulfate	‡	2	5	8	6	2	5‡

* "Triton × 500" is a clear, syrupy liquid, which when diluted to 1 per cent with distilled water becomes cloudy. This cloudiness, however, does not affect its efficiency.

† The eyes sting after a few instillations in some patients.

‡ The check on rabbit eyes showed from slight to considerable capillary congestion. In spite of this poor result in the rabbit, we used the drug on human eyes, with some stinging but without disastrous results.

Occasionally tween 80® and triton X500® gave a momentary sting when instilled in the eye. Possibly the most effective surface-active agents were in the order named: triethanolamine, triton 720® and triton A20.®

Pilocarpine Hydrochloride, 0.5 per cent (table 2).—One hundred and thirty-eight patients were examined. Previously, the pilocarpine had been poorly borne, especially when used in treatment of glaucoma, but not when used to contract the pupil after the use of a mydriatic. The results here obtained, however, were quite different. The patients included 12 patients operated on for glaucoma who were comfortable, except for a man, for whom triton X500® was used. This man had edema of the lids and severe pain, but he persisted in use of this drug for fourteen days despite the discomfort. The results with the other 11 patients were so encouraging that we even used pilocarpine in tween 80® in reducing ocular pressure, even though we knew from the

laboratory studies that the rabbit eyes showed capillary congestion after its use.

Contraction of the pupil and control of ocular pressure were best accomplished when triethanolamine, triton A20® and triton X200® were used.

Eucatropine Solution, 0.5 per cent (table 2).—Thirty-eight patients were treated with combinations of this drug. Even though the rabbit eyes were not affected by this combination, 3 of our 5 patients for whom tween 80® was used complained of pain. Some patients had instillations of all the seven combinations of surface-active drugs and eucatropine in each eye, with no ill effect.

Full dilation, but with reaction to light and ability to read, was obtained with only 1 patient, for whom triton X200® and tween 80® were used. This patient was 70 years old and had hazel eyes. Most patients, however, obtained a maximum pupillary diameter of 4 to 5 mm.

Homatropine Hydrobromide, 0.5 per cent.—There were 28 patients in this group. Because it was felt that homatropine would be difficult to neutralize if there were severe congestion, it was decided not to use a solution of this drug in the surface-active agents which demonstrated conjunctival irritation in the rabbit eye (table 2).

The rapidest dilation was obtained with the following wetting agents, in the order indicated: triton 720,® triton A20® and, lastly, triton X155.® Full dilation was obtained in from thirty to fifty-seven minutes. A few patients showed reaction to light, and several could read in full mydriasis. Three gave evidence of cycloplegia. Three drops was the greatest number used.

Atropine Sulfate, 0.5 per cent.—Twenty-eight patients were treated with combinations of this drug. The results were not encouraging. It is possible that, since the dose was small (0.5 per cent) and atropine takes a long time to act, the first drop has spent itself before the second drop was instilled. It was much more difficult to obtain full dilation with this drug than with homatropine.

Of the few wetting agents in this group, possibly the best results were obtained with tritons X200,® X155® and A20.® In 1 case, triton 720® instilled in one eye and triton A20® in the other gave full dilation in twenty minutes. In some cases there was no reaction to light and the patient could not read. On no case could a test for cycloplegia be made. The patients for whom atropine was used had a corneal ulcer or iritis or their cooperation was unreliable because of their extreme youth.

SUMMARY AND CONCLUSIONS

Surface-active agents are often called wetting or penetrating agents. Because of these qualities, they were suggested for use as vehicles, in common with many ophthalmic drugs.

There are over a thousand of these preparations now in use, and they are suitable for a host of purposes, from toothpastes to automobile greases. A large majority are much too irritating to be used in ophthalmologic practice.

To evaluate these drugs, we tested a number on rabbit eyes, and then on patients. We also checked the agents bacteriologically to determine their bacteriostatic action. It was found that certain wetting agents had no deleterious effect on the eye, but became irritating only when combined with certain ophthalmic drugs.

A new preparation, hyamine L4-669,® similar to benzalkonium zephiran® chloride, was proved to be valuable as an antiseptic by laboratory and bacteriologic studies and by clinical use in treatment of infections in the human eye.

A 3 per cent solution of sulfathiazole in triton X155® instilled in the eye of a rabbit at frequent intervals for several days did not appear in the primary or the secondary aqueous. An effort will be made to repeat this study with other surface-active agents. Over 1,000 patients have been studied.

A 1 per cent solution of the surface-active agent as a vehicle was used with such drugs as 0.5 per cent atropine sulfate, homatropine hydrobromide, eucatropine hydrochloride, tetracaine hydrochloride and paredrine hydrobromide ophthalmic.® Many proved fairly effective. The relative therapeutic effect of the various combinations is given. Good results appear to be obtained when the p_H of the surface-active agent ranges from 8 to 9.

At present no method of standardizing surface-active agents is known, and one batch of material may differ slightly from another. This difficulty will be overcome in due time.

The new mydriatic dibutoline sulfate (dibutylcarbonate of dimethyl-ethyl-2-hydroxyethylammonium sulfate), 5 per cent, is surface active. The effectivity of tetracaine has been explained by its surface activity.

Recently, Hauser and associates,[21] in their work with sodium penicillin, called attention to the fact that this preparation is surface active—a property which possibly accounts for the excellent results obtained by its use. Chemical manufacturers are usually cooperative, and it is felt, with their assistance, a large number of vehicles will become available for use in ophthalmology.

37 South Twentieth Street.

21. Hauser, E. A.; Phillips, R. G., and Phillips, J. W.: Science **106**:603, 1947.

OPERATION FOR CONGENITAL CATARACT

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THE SUBJECT of congenital cataract is given relatively little space in textbooks of today. The traditional treatment of needling or discission, often repeated, is generally employed. Needling is open to many serious objections, such as the danger of chemical irritation and secondary glaucoma, which not uncommonly necessitates further operation on a highly inflamed eye. Other objections are protracted convalescence; the frequent necessity of repeated discission in order that resorption may be complete, and delayed restoration of vision in young subjects, with resultant amblyopia. Retinal detachment not uncommonly occurs in adult years as a result of repeated discission in early childhood. Ziegler recommended the through and through incision, hoping to prevent secondary glaucoma. According to Spaeth,[1] a through and through incision of the lens into the vitreous is not a guarantee against the development of secondary glaucoma; instead, damage may occur to the vitreous, with later development of iridocyclitis of chronic type, and even retinal separation.

Elschnig[2] recommended removal of the lens by "linear extraction" at the age of 3 months for the relief of total cataract and at the age of 6 months or later for partial cataract. Because of its danger, "linear extraction" was not generally accepted. A technic of "linear extraction," modified to avoid the danger and to permit safe removal of congenital (and membranous) cataract in infancy, as well as later, was suggested by me[3] in 1931. Its favorable aspects were confirmed by Green and Beisbarth.[4] Additional

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1. Spaeth, E. B.: The Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1939, p. 545.

2. Elschnig, A.: Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, W. Engelmann, 1908, p. 1192.

3. Barkan, O.: A Procedure for Extraction of Congenital, Soft and Membranous Cataracts, Am. J. Ophth, **15**:117-124 (Feb.) 1932.

4. Green, J., and Beisbarth, C.: Extraction of Congenital and Young Adult Traumatic Cataract by the Method of Barkan, Am. J. Ophth. **16**:603-606 (July) 1933.

modifications which have since been introduced are described in the present article. The essence of the procedure is to dilate the pupil maximally with atropine instilled for four days prior to operation and again with epinephrine hydrochloride U. S. P. (1 : 1,000) injected subconjunctivally at operation. Thus the margin of the pupil comes to lie peripheral to the inner lip of the wound of the keratome incision. The incision is made obliquely in the cornea 1 to 1.5 mm. axial to the corneoscleral border, and in a plane parallel to that of the iris. Designed as a trapdoor, or valve, incision, which is watertight and airtight as regards the contents of the anterior chamber, it prevents the outflow of fluid or air and encourages rapid reformation of the chamber. This effect, combined with maximal dilation of the pupil and the hypotony induced by epinephrine (dynamic, since it is due partly to stimulation of the sympathetic nerve fibers), tends to prevent the iris from contacting or adhering to the inner lip of the wound. Since anterior adhesion of the iris occurred, nevertheless, in some cases, a precautionary measure was instituted. This consists of postoperative reestablishment of the anterior chamber by means of injection of isotonic sodium chloride solution through a prelaid corneal puncture. The patient leaves the operating table with the chamber fully reformed. Since this modification has been added to the original procedure there has been no instance of anterior adhesion. Dr. F. C. Cordes recently reported the injection of a bubble of air after operation for the same purpose. The bubble is so placed by positioning of the head that contact of the iris with the inner lip of the wound is less likely. Introduction of the bubble of air may be combined with the injection of saline solution.

In case a secondary membrane forms, it is suggested that needling or discission be avoided. If the membrane is delicate, it may be removed by gentle traction with the smallest type of capsulectomy forceps. If thick and tightly adherent, it may be cut at right angles to the line of traction with Barraquer scissors. Both maneuvers can be performed with a high degree of safety by the surgical technic already outlined.

The absence of complications and the smooth convalescence are in striking contrast to the delay and complications of discission. The establishment of clear media in early infancy is advantageous. No late complications, such as retinal detachment, has been encountered. There has been no case of sympathetic ophthalmia.

In the case of binocular total cataract it is suggested that surgical intervention begin when the infant is 3 months of age. After successful surgical treatment of one eye, the other eye should be operated on without delay. In my experience, corrective glasses have been worn after operation with satisfaction in several cases at the age of 4 and

5 months. Since experience has shown that no useful purpose is accomplished by early operation in cases of monocular cataract, it is recommended that surgical treatment be deferred in such cases until a later age, when full cooperation of the patient is obtainable.

SURGICAL PROCEDURE

A drop of 1 per cent solution of atropine sulfate is instilled in the eye to be operated on once a day for four days. Examinations, including a roentgenographic study of the chest for enlargement of the thymus, are carried out in all cases. With

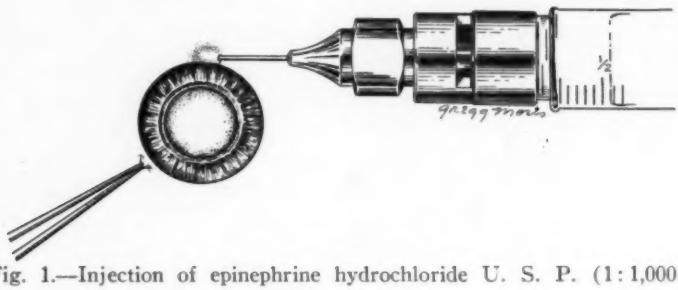

Fig. 1.—Injection of epinephrine hydrochloride U. S. P. (1:1,000).

infants the usual diet is maintained up to six hours prior to operation; sugar solution is forced up to four hours to avoid dehydration with associated hyperpyrexia.

General anesthesia is used with infants and with children of ages up to 12 or 14 years. In view of the delicacy of the operation as applied to infants who may be only a few months old, and who may show other congenital defects, the importance of the anesthesia cannot be overemphasized. An injection of atropine is given forty-five minutes before operation. Ether is administered through a

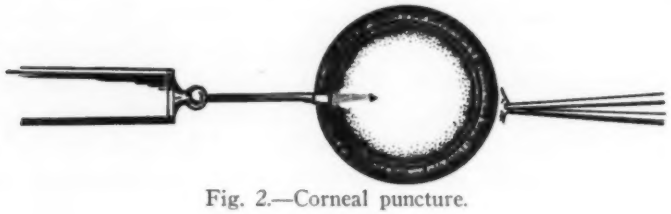

Fig. 2.—Corneal puncture.

suitably small airway. Since the face is covered with an eye sheet and the operation may prove lengthy, a generous supply of oxygen should be assured at all times.

Before the operator scrubs and the patient is draped, 2 to 4 minims (0.124 to 0.248 cc.) of epinephrine hydrochloride U. S. P. (1:1,000) is injected at several points along the upper limbus with a no. 30 needle ½ inch (1.27 cm.) in length (fig. 1) attached to a 1½ inch (3.8 cm.) Luer syringe. The intraocular action is increased by injecting as close as possible to the corneoscleral border. The injection is facilitated by inserting the needle with the opening facing the bulbus when puncturing the conjunctiva. It is best to inject the major portion at 12 o'clock in the meridian contiguous to the point of corneal incision. Akinesis is

induced and a retrobulbar injection of 2 per cent procaine is given and the eye is prepared in the usual manner. The face mask should be of moistened gauze in order that it may be easily molded to the region.

After ten to fifteen minutes the pupil is maximally dilated, so that it almost disappears behind the limbus and hypotony has developed. The dilation, being due to a contraction of the sympathetic dilator fibers, is tonic, in contradistinction to the paralytic dilation of atropine. The iris consequently maintains an exaggerated contractility, which keeps it retracted from the wound and prevents its prolapse. The hypotony of the bulbus induced by epinephrine is such that the usual tendency of the ocular contents to prolapse is greatly reduced. This tendency is further discouraged by making the keratome incision oblique and within the cornea.

Adequate exposure is provided by canthotomy and by lid sutures, six to eight in number, of 000000 black silk placed along the ciliary margins of the upper and lower lids. The sutures are held with mosquito forceps. The superior rectus is controlled by a bridle suture of 000000 black silk.

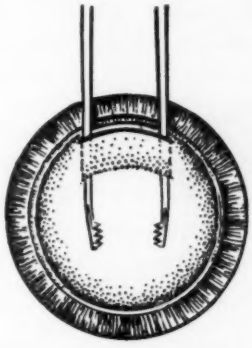

Fig. 3.—Corneal incision and capsulectomy forceps

Illumination and magnification are important. In the cases of membranous cataract, the focal illuminator will eliminate annoying reflections.

A corneal puncture is made in preparation for the later deepening of the anterior chamber, the blade being placed extremely tangentially, 1 mm. axial to the corneoscleral border at 9 o'clock on the right eye and at 3 o'clock on the left eye, after the site has been touched with an applicator previously dipped in tincture of iodine (fig. 2). A discission knife which has been dipped in fluorescein to mark the position of the puncture is used, the bulbus being fixed by a Bishop Harman forceps at the opposite limbus. The wound canal should be at least 2 mm. long, so that it will be air and water tight. The tip of the knife should barely perforate Descemet's membrane, as observed through a head loupe. It may be necessary to tip the blade backward a little in order to perforate the membrane. Care should be taken not to enlarge the puncture on removing the knife.

The corneal incision is made with a keratome at 12 o'clock, 1 to 1.5 mm. axial to the corneoscleral border. It is placed obliquely to the corneal surface and parallel to the plane of the iris, thus forming a valve, or trapdoor, incision, which tends to close more tightly, the greater the pressure within the anterior chamber. It should be no larger than necessary for the extraction of the lens

matter or membrane, as the case may be. Excessive obliquity may interfere with freedom of intraocular instrumentation, but the size and obliquity can be adapted to the needs of the individual case in order to achieve an optimum of freedom of instrumentation, deliberate manipulation, security of healing and elimination of hazards (fig. 3).

A number of instrumental procedures have been described for the extraction of the various forms of congenital cataract and membranes. It is beyond the scope of this paper to more than touch on them. Depending on the type of cataract or membrane to be operated on and the individual operator's preference, capsulectomy forceps, cystotome, narrow Hess shovels, irrigation, blunt hook or small, delicate Barraquer scissors may be used. The various types of congenital cataract and their surgical implications have recently been described in a comprehensive review of the subject by Dr. Cordes.[5]

At the end of the operation the anterior chamber is deepened in the following manner: The corneal puncture, which was prelaid with a discission knife and stained with fluorescein, is touched with a dry applicator and with one dipped in tincture of iodine. With a no. 30 needle (previously drum tested or examined under a loupe to assure its having a perfect point) attached to a 1.5 cc. Luer syringe, saline solution is injected, the surgeon fixing the bulbus at the contralateral portion of the limbus (fig. 4). Air may be injected in the same manner.

Fig. 4.—Deepening of the anterior chamber.

It is important for the patient to leave the operating table with the anterior chamber deep.

The usual measures for postoperative care, consisting of use of binocular pads, eye shield and arm restrainers, are observed. Elixir of phenobarbital is administered.

SUMMARY

The traditional treatment of needling or discission of congenital cataract or membrane is open to many serious objections. Removal of the cataract by a modified form of linear extraction is recommended. The technic is described. Recent modifications are given which further assure extraction without hazard in early infancy.

490 Post Street (2).

5. Cordes, F. C.: Surgery of Congenital Cataracts, Am. J. Ophth. **31**:1073-1084 (Sept.) 1948.

CHOROIDORETINAL DEGENERATION

A SEX-LINKED FORM IN WHICH HETEROZYGOUS WOMEN EXHIBIT A TAPETAL-LIKE RETINAL REFLEX

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THE TAPETUM lucidum, an iridescent cellular or noncellular layer of the choroid, which is responsible for the metallic reflex seen at night in the eyes of many mammals, is not present in the human eye. However, in rare instances a tapetal-like retinal luster has been observed ophthalmoscopically. In the 2 cases described by Mann [1] the abnormality occurred in women and was unaccompanied with any impairment of vision. Concerning one of these women, it was said that in childhood "her eyes used to glow in the dark like an animal's." Dr. Mann's patients were not known to be related, and their families were not investigated.[2] To our knowledge, only 1 other instance of a tapetal reflex has been mentioned in the ophthalmologic literature, this being the case of a woman described by Niccol.[3]

During the course of a genetic study which originated with a 30 year old man who exhibited an atypical form of retinitis pigmentosa, an unusual appearance of the fundus was discovered in the man's mother and in one of the latter's sisters. The anomaly seen in these women closely resembled that described by Mann [1] in the case represented by her figure 105. Further investigation revealed the occurrence of additional cases of both retinitis pigmentosa and the tapetal-like condition in such a way as to suggest the operation of a sex-linked gene producing retinitis pigmentosa in males and the tapetal-like reflex in heterozygous females. Because of practical, as well as theoretic, interest attaching to this unusual form of eyeground, it is proposed to describe the family in detail.

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1. Mann, I.: Developmental Abnormalities of the Eye, Cambridge University Press, 1937.

2. Mann, I.: Personal communication to the authors, London, 1946.

3. Niccol, W.: A Family with Bilateral Developmental Defects at the Macula, Tr. Ophth. Soc. United Kingdom **58**:763-769, 1938.

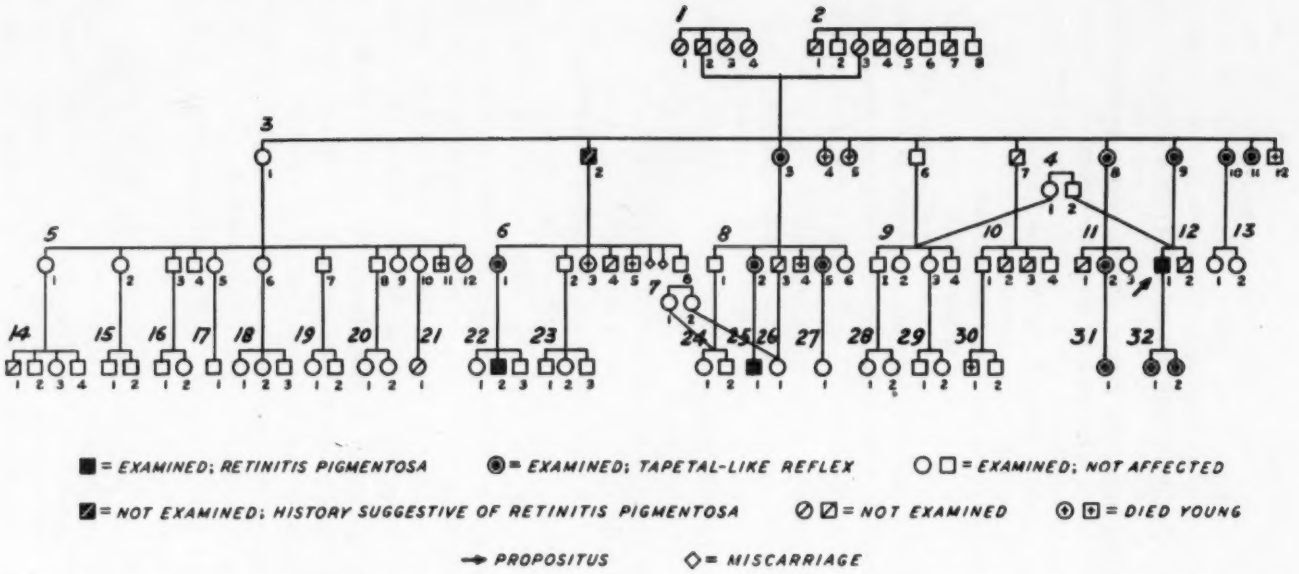
■ = EXAMINED; RETINITIS PIGMENTOSA
◉ = EXAMINED; TAPETAL-LIKE REFLEX
○ □ = EXAMINED; NOT AFFECTED
◪ = NOT EXAMINED; HISTORY SUGGESTIVE OF RETINITIS PIGMENTOSA
⊘ ⊡ = NOT EXAMINED
⊕ ⊡ = DIED YOUNG
→ PROPOSITUS
◇ = MISCARRIAGE

Fig. 1.—Heredity chart of kindred 776 of the Heredity Clinic of the University of Michigan, showing a sex-linked form of choroidoretinal degeneration in which heterozygous women exhibit a tapetal-like retinal reflex.

This family constitutes kindred 776 in the files of the University of Michigan Heredity Clinic. The pedigree presented in figure 1 shows 105 relatives of the propositus, of whom 75 were examined in their homes or at the ophthalmic clinic of the University Hospital. The spouses of these subjects were also examined in almost all cases and were found to be normal with respect to the two abnormalities under study. The spouses have therefore been omitted from the pedigree chart except in cases in which they were known to be related *inter se,* producing double first cousin relationships. In the following sections of the paper, each individual member will be identified by means of a double number, the first number designating the sibship, as indicated by the number above the sibship line in figure 1, and the second designating birth order within the sibship, as shown by the number beneath the individual's pedigree symbol. Thus, the propositus, or original patient, is *12-1,* and, as is seen in figure 1, his daughters are *32-1* and *32-2.* The spouses will be identified by adding the letter *a* to the number of the espoused. Thus, the wife of *12-1,* who is not shown in the diagram, will be designated as *12-1a.*

On the hypothesis of sex-linked inheritance, the gene responsible for the disease present in this family must have been derived from *2-3,* the mother of sibship *3.* Beyond this point its origin is problematic. Three of *2-3*'s brothers, *2-2, 2-6* and *2-8,* were living. Examination of these men revealed good visual acuity, normal color vision and absence of fundic changes suggestive of retinitis pigmentosa or related defects. Numerous descendants of *2-1, 2-2, 2-4, 2-6* and *2-8* were examined, without further trace of the two anomalies in question. Only 1 member of sibship *2* was reported to have had "bad eyes," namely, *2-7.* He was said to have been extremely near-sighted from childhood, but he did not complain of night blindness; he died at the age of 50, leaving no children. The parents of sibship *2,* C. P. (father) and W. E. (mother), resided near Breslau, Germany. After the latter's death the family emigrated to America, settling in Brown County, Wis.

SUMMARY OF OCULAR FINDINGS

A description of the ocular histories and abnormalities of the fundus of the propositus (*12-1*) and his mother (*3-9*) will be presented first. The left fundus of *12-1,* showing retinitis pigmentosa, is depicted in figure 2 *A,* while the corresponding fundus of a maternal aunt *(3-10),* showing the typical glistening golden verruciform, or "tapetal-like" change, is shown in figure 2 *B.* In these 2 subjects, as in other affected members of the kindred, the two eyes were rather symmetrically involved. However, interesting variations were observed between the eyes of various other affected persons, and we shall therefore add somewhat briefer descriptions of the other affected members. In addition,

a few cases will be cited in which we encountered ocular abnormalities which were probably unrelated to the disease under investigation. These cases will serve to illustrate the fact that examination of any large kindred is likely to disclose a variety of ocular anomalies, which might easily lead to erroneous genetic interpretation if hearsay information alone were accepted.

12-1.—O. P., a man aged 30, who served as the propositus for the family investigation, was first seen at the University of Michigan Hospital on Dec. 11, 1945. His chief complaints were night blindness and ease of ocular fatigue. The patient's uncorrected visual acuity was 2/60 in each eye. With his own correction visual acuity was 6/30 in the right eye and 6/15+1 in the left eye. External ocular examination showed a normal condition except for an alternating divergent strabismus, which measured 10 degrees (Priestley Smith). The pupillary reflex was normal in both eyes. The irides were blue with considerable brown around the pupillary margins.

Funduscopic examination revealed a small area of centrally placed posterior subcapsular cataractous change in each lens. There were numerous opacities in the vitreous. The optic disk in each eye was somewhat indistinct, as a result of moderate glial infiltration. The choroidal circulation was vividly seen throughout the entire fundus in each eye. It was most conspicuous in the vicinity of the optic nerve head and at the retinal periphery. Not illustrated in the drawing (fig. 2 *A*), but visible ophthalmoscopically, were a few choroidal vessels showing evidence of early sclerotic change. The retinal arteries and veins were both somewhat reduced in caliber. There was no evidence of arteriolar sclerosis. As shown in figure 2*A*, the pigment in the immediate vicinity of the fovea and the macula retained some of its normal characteristics, except for stippling and mottling. Temporal to the disk the pigment was clumped in small, irregular masses. The entire retina, with the exception of the macula, was conspicuously atrophic. The retinal pigment had migrated into the substance of the retina and had become arranged in strands and clumps. In some areas it had apparently piled up in the perivascular spaces. The fundi were very similar except for minor variations in deposition of pigment.

With standard clinical illumination and a 5/330 test object, the visual fields were found to be concentrically constricted to within 5 degrees of the fixation point. Color vision was normal (Ishihara, seventh edition). Tonometric tension was 24 mm. of mercury bilaterally (new Schiøtz method).

Refraction gave the following correction: right eye: —2.75 sph. ⊃ —2.00 cyl., axis 11, vision 6/30; left eye: —2.25 sph. ⊃ —2.50 cyl., axis 172, vision 6/15+. Measurements of muscle function showed 3 degrees of left hyperphoria for distant vision (right eye) and 2 degrees of left hyperphoria with 16 degrees of exophoria in accommodation (left eye).

3-9.—Mrs. E. H. P., the mother of the propositus, was first examined at the age of 47, when she accompanied her son on one of his clinical visits. She specifically stated that she did not have trouble with vision in the dark, but complained of minor asthenopic symptoms. On Jan. 22, 1946 visual acuity was 4/60 in each eye. Refraction with paredrine and homatropine cycloplegia gave the following correction: right eye: +4.25 sph. ⊃ +1.25 cyl., axis 92, vision 6/6; left eye: +4.25 sph. ⊃ +1.25 cyl., axis 90, vision 6/6. Measurements of muscle function revealed a minimal convergence insufficiency. The irides were blue with brown pupillary borders. The remainder of the external ocular examination revealed nothing significant.

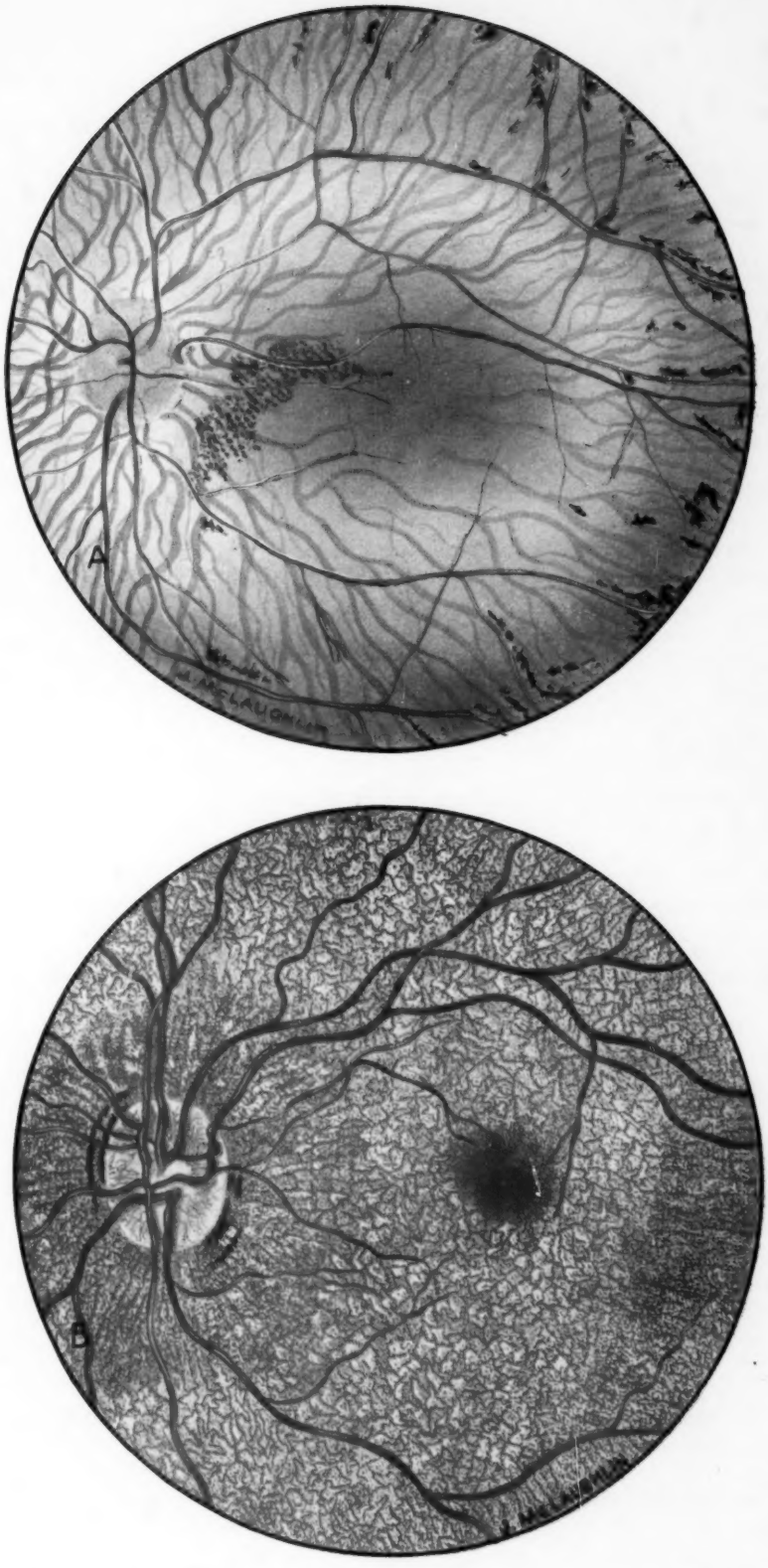

Fig. 2.—*A*, left fundus of *12-1*, showing retinitis pigmentosa; *B*, left fundus of the maternal aunt (*3-10*), showing the tapetal-like change.

Funduscopic examination showed that the lens and central media were clear in both eyes, except for a few strandlike opacities in the vitreous. The disks were normal in size and color and were oval vertically. The retinal vasculature was normal except for a slight reflex striping of the arterioles. There was a good foveal reflex in each eye, and the macular pigmentation was normal. However, scattered in and about the macular area were numerous dustlike, golden, glittering bodies. With the binocular ophthalmoscope these bodies were seen to be deep to the retinal vessels and seemingly were obscured by the increased pigmentation at the macular center. Because of these two features, it was concluded that they probably represented minute verrucae or drusen. They were so numerous in specific areas as to become conglomerate and apparently formed irregular masses. When specific details were not fixated, the impression was that of a golden yellow sheen, not unlike that seen in certain mammalian fundi. The verruciform structures were most numerous just outside the macular area and faded out gradually into the retinal periphery. There was no suggestion of a pathologic condition of the retina except for the presence of occasional small areas of depigmentation in the extreme periphery. There was no essential difference between the two fundi.

Tonometric tension was 21 mm. of mercury bilaterally (new Schiøtz method). Visual fields, measured in the usual clinical manner with a 2/330 test object, showed a minor contraction of the field temporally and inferiorly in each eye. The blindspots were normal in size, and there was no evidence of central scotoma. Color vision was normal (Ishihara). The Kahn reaction of the blood was negative.

1-2.—W. H., the elder, the maternal grandfather of the propositus, had died at the age of 89, in 1945. According to his relatives, he first complained of loss of vision at the age of 60, but no statements concerning night blindness could be recalled. During the last three or four years of life he was said to have been totally blind. Dr. E. S. Schmidt, of Green Bay, Wis., furnished us the following facts: "Mr. W. H. consulted me on Jan. 22, 1919, with vision of 8/200 in the right eye and of 5/200 in the left eye. At that time he complained of seeing through a fog all the time. The disks were pale and had a pearly look." No other abnormalities were visualized in the fundi at that time. A Wassermann test was not performed. It was Dr. Schmidt's impression that the patient had primary atrophy of the optic nerve of unknown cause. In accordance with the mode of inheritance postulated here, i.e., sex linkage, he would not have been expected to possess retinitis pigmentosa, inasmuch as he possessed a daughter (*3-1*) lacking the heterozygous manifestation and a son (*3-2*) who was presumably affected.

3-2.—W. H., the younger, had died at the age of 56, in 1942, and information concerning him was obtained solely through his wife and a local optician. The latter possessed a pair of glasses worn by the patient containing a —6 D. sphere for the right eye and a —8 D. sphere for the left eye. According to his wife, he had been sent home from school at the age of 10 because he needed glasses. Vision failed progressively, and during the last years of life he was said to have been almost totally blind, being able to see objects only when they were directly in front of him. He consistently refused to consult an oculist. On the pedigree chart (fig. 1) we have chosen to regard him as probably affected with retinitis pigmentosa.

3-3.—Mrs. P. J. P., a moderately obese woman aged 61, was the oldest woman examined among the known carriers, or heterozygotes. An unusual amount of melanin pigment was present in the skin of the eyelids bilaterally. There was considerable scarring of the face, which was attributed to roentgen burns resulting from treatment for hirsutism of the upper lip. She had never worn glasses and

expressed no difficulty with reading or ocular discomfort of any kind. Uncorrected vision was 6/9 in the right eye and 6/12 +1 in the left eye. External ocular examination was noncontributory except for moderate lateral deviation under cover and minimal arcus senilis bilaterally. The central media were clear except for occasional opacities in the vitreous. The disks were normal, but a moderate degree of circumpapillary retinal atrophy was present. A good foveal reflex was noted in both macular areas. The typical verruciform golden appearance of the fundus previously described was present. It differed from that to be described for the patient's younger sisters in that the supposed verrucae were somewhat larger, and possibly less numerous. The retinal arterioles showed mild, sclerotic changes, but no unusual degree of choroidal arteriosclerosis could be seen. The retinal periphery disclosed a few scattered areas of depigmentation, bordered by thin rings of accumulated pigment. There was no evidence of inflammatory disease. In the confrontation test, the fields showed minimal peripheral constriction, which was slightly more pronounced in the left eye. Subjectively, however, the patient was unaware of any handicap in the dark, as in walking about the yard at night or on entering a dark moving picture hall in the daytime.

3-8.—Mrs. B. D., a blonde woman aged 50, had no ocular complaints. Uncorrected visual acuity was 6/9 —1 in each eye, and she could easily read ordinary newsprint with a +2.00 spherical lens. The skin of the lids was finely wrinkled and somewhat thin for a woman of her age. Some minor facial asymmetry was present, the left orbit being slightly higher than the right. The left half of the face was also noticeably narrower than the right. The cover test disclosed exophoria. Mild arcus senilis was seen in both corneas. The anterior chambers, irides and pupillary reflexes were normal. The central media were clear. The disks showed high central branching with structural blurring of the margins. The foveal reflex was well seen in both eyes. Extensive minute verrucae, so fine and conglomerate as to give the impression of gold dust, were seen throughout the fundi, except in the extreme retinal periphery. The heaviest concentration appeared just outside the macular reflex ring. In the retinal periphery of the right eye, in the 9:00 o'clock meridian, was a disk-sized area of depigmentation. No glial or pigmentary clumping was noted in association with the latter. Two such depigmented areas were noted in the temporal periphery of the retina in the left eye. The choroidal and retinal vasculatures appeared normal. Intraocular tension appeared normal on palpation. Confrontation tests showed normal fields. Color vision was normal (Ishihara test).

3-10.—Mrs. R. D., a well developed woman aged 45, had no specific ocular complaints. She denied having night blindness. Uncorrected visual acuity was 6/6 —2 in the right eye and 6/6 —3 in the left eye. External ocular examination showed a normal condition except for minor lateral deviation under cover. The pupillary reflexes were normal. Funduscopic examination revealed no pathologic changes except for the presence of occasional opacities in the vitreous of each eye. The disks were normal in size and color, and the retinal vasculature was normal. An excellent foveal reflex was seen in the macular area of each fundus. Retinal pigment was normal and of only moderate amount. Appearing in and about the macular area were a myriad of small yellow, glistening deposits, which were deep to the retinal vessels. Their density decreased as one approached the retinal periphery. The left fundus is illustrated in figure *2 B*; the picture in the right eye was very similar. Although the central portions of the fundi presented a golden, glittering appearance as seen with the ophthalmoscope, the reflex from the fundus appeared normal in intensity and hue when viewed from a distance in a darkened room.

The visual fields appeared normal in the confrontation test. Palpation revealed normal intraocular tension bilaterally. Color vision was normal (Ishihara).

3-11.—Mrs. W. E., aged 41, who was without children, was studied by Dr. Raymond C. Warner, of Milwaukee. On the basis of his report, we unhesitatingly classify her as a fifth heterozygous female in sibship 3.

"There was no history of ocular injury or inflammation and no ocular complaints other than a slight blurring of vision for a short time after awakening in the morning. There was no night blindness. The patient had never worn glasses. The irides appeared normal and were blue. External ocular examination showed nothing significant. Examination with the slit lamp disclosed a faint discoid shadow in the posterior pole of the left lens, but no classification was possible. The central media and lenses were otherwise clear.

"On dilation, the pupils were round and equal. Funduscopic examination of the right eye revealed an irregular, round disk, with very high central branching. There was venous pulsation in the cup, which was funnel shaped, with a deep physiologic depression. The lamina cribrosa was faintly seen. Rings of pigment were present, with an increase in the pigmentation temporally. The retinal arteries and veins appeared somewhat smaller than average, but the ratio was 4:5. The entire macular area presented a glistening, golden, wartlike appearance. The foveal reflex was present. These golden granules were confined almost entirely to the macular area, with little evidence of their existence toward the periphery. The left fundus was very similar to the right, but the central gold. glittering, granular change in the macular area was more pronounced than in the right eye and somewhat more extensive in its distribution. One gained the impression of ripples of golden sand distributed over a reddish background. No peripheral lesions were seen in either fundus.

"Intraocular tension was normal to touch in both eyes. Visual acuity without correction was 6/6 —2 in the right eye and 6/6 —1 in the left eye. Retinoscopic study showed a correction of + 1.50 sph. ⌒ + 0.50 cyl., axis 110 in the right eye and of + 1.50 sph. ⌒ + 0.25 cyl., axis 110 in the left eye. Corrected vision was 6/6 in the right eye and 6/6 —1 in the left eye."

With a 5/330 test object, the visual fields showed only minor peripheral constriction in the left eye. Measurements of muscle function were within normal limits.

6-1.—Mrs. N. R., aged 34, asthenic and moderately dark-complexioned, occasionally experienced asthenopic symptoms in association with close ocular work but denied having night blindness or progressive visual failure. Uncorrected visual acuity was 6/9 —2 in the right eye and 6/30 in the left eye, correctable to 6/6 in each eye. The results of external ocular examination were without significance except for a moderate overshoot of the left eye when she was looking up and to the right. The near point of convergence was 115 mm., and there was considerable lateral deviation under cover. The central media, disks and vessels were normal in both eyes. A glistening, golden granular reflex was present throughout the retina and extended almost to the extreme periphery. A few patches of retinal depigmentation, measuring from ⅛ to ¼ disk diameter, were noted in the extreme nasal and temporal peripheries of each fundus. These patches were oval or round. No specific clumping of pigment could be seen. Intraocular tension was normal to palpation, and the fields were normal as tested by confrontation. Color vision was normal (Ishihara).

8-2.—Mrs. H. Ch., aged 35, had fundi showing the typical tapetal-like reflex and her only child was a boy (*25-1*) having retinitis pigmentosa. She denied having any ocular symptoms, particularly with respect to night blindness or pro-

gressive loss of vision. Uncorrected visual acuity was 6/9 —1 in the right eye and 6/6 in the left eye. Some facial asymmetry was noted, the left orbit being slightly higher than the right. External ocular examination was without significance except for mild blepharitis marginalis sicca and the presence of slight overshooting of the opposite eye when she was looking up to the right or to the left. The central media were clear, except for a few strandlike opacities in the vitreous. The disks were normal, and a good foveal reflex was seen in each macula. The golden, glistening change was seen throughout the fundus except in the extreme periphery of each eye. In the peripheral areas there were several smaller and some larger areas of moth-eaten retinal atrophy or pigmentary mottling and some rather large verrucae, but no clumping of the bone corpuscle type. The choroidal vessels were vividly seen, and there was no evidence of arteriosclerosis of either the retinal or the choroidal vasculature. The fields were full as tested by confrontation. Color vision was abnormal, as will be described in a later section.

8-4.—N. P., a boy aged 10 years, according to his parents, became completely blind during the last few months of his life and died of convulsions on Nov. 30, 1924. Dr. C. W. Rucker furnished the following information:

"The patient registered at the Mayo Clinic on June 12, 1924, at the age of 10 years. At that time he had symptoms of a cerebellopontile tumor. Surgical exploration was advised, but permission was refused by the father. There are no follow-up notes on our findings, for the boy was apparently taken home and died there six months later. Ophthalmologic examinations conducted here on June 13 revealed that the pupils and pupillary reflexes were normal. The fields appeared full on a rough test. There were choking of both optic disks and elevation of 3 D. Since such patients are examined with the use of homatropine mydriasis, the examining physician had a good look at the fundus, and to him it appeared normal, with no evidence of retinitis pigmentosa."

Because of the boy's early death, we have chosen to regard the condition of this child as "unknown" and to exclude the case for statistical purposes.

8-5.—Mrs. O. L., aged 31, had the typical golden, granular appearance of the fundi, but she did not complain of any visual difficulty or ocular discomfort. While at first admitting that she had difficulty in seeing at night, she was not definite about this; moreover, she was the only woman who mentioned any difficulty of this kind. The uncorrected vision was 6/4.5 —3 in each eye. The pupillary reflex was normal bilaterally. Extraocular movements were normal except for a definite overshooting of the left eye when she was looking up and to the right, but no hyperphoria was demonstrated with the cover test. Medium-sized medial pingueculae were present bilaterally. The central media were normal. The disks were normal, and a good foveal reflex was seen in each eye. The glittering, golden, verruciform bodies in the choroid or retina appeared to be more concentrated about the disks and macular areas in this patient than in other affected women. There were some pigmentary washing and faded mottling (depigmentation) in the periphery of each eye, and a disk-sized area of atrophy was noted in the periphery of the left fundus at 3:00 o'clock. No glial changes or perivasculitis was observed. The choroidal and retinal vessels were normal. With the confrontation test the fields seemed normal. The same form of anomalous color vision found in *8-2* was present in this patient.

9-1.—O. R. H., a man aged 29, was reported to have severe visual difficulty, but examination revealed no signs of the choroidoretinal disease under investigation. According to Dr. E. S. Schmidt, the patient had had purulent conjunctivitis of both eyes, which was treated at the age of 4 weeks, with residual corneal opacification. Our examination in 1946 showed right hypertropia. The eyes

were straight in the primary position, and there was horizontal nystagmus with occasional vertical and rotatory components. The cover test also showed a lateral right divergent strabismus of approximately 15 degrees. The right cornea showed a macular scar of 4 mm., which encroached on the visual axis from below, and a similar scar was present in the left cornea, but was nebulous. An anterior polar cataract was present in the right eye, the lens of the left eye being clear. The fundi were normal except for situs inversus vasorum in each eye. Uncorrected vision was 1/60 in the right eye and 6/21 in the left eye, and the patient wore correction for an extensive hyperopic astigmatism. Color vision was normal (Ishihara). The maternal grandfather was said to have had poor vision and nystagmus.

11-2.—Mrs. G. D. W., aged 26, disclaimed having symptoms suggestive of night blindness and had no ocular complaints. Uncorrected visual acuity was 6/6 —4 in the right eye and 6/6 +3 in the left eye. The cover test disclosed definite convergence, but the eyes were straight in the primary position. The pupillary reflexes were normal. The central media were clear except for a few strandlike opacities in the vitreous of the left eye. There was an excellent foveal reflex in the macular area of each fundus. The golden, tapetal-like reflex was present in both retinas, mostly concentrated in and about the disk and macular area and thinning out toward the periphery. There was some moth-eaten mottling of the pigment in the periphery of each eye. Intraocular tension was normal on palpation. Confrontation tests revealed normal fields. Color vision was normal (Ishihara).

22-2.—N. D. R., a boy aged 12, of slender build, had had mumps and erysipelas at the age of 1 year. At about this time the parents also were aware that the child was extremely near-sighted. He complained of night blindness after starting to school, at the age of 6 years. Examination at the age of 4 years by A. N. Abbott, D.O., revealed a "peppery fundus" in each eye, and vision was recorded as 10/200 for both eyes. Retinoscopic examination indicated a correction of —6.75 sph. ⌒ —1.75 cyl., axis 15 for the right eye and —7.00 sph. ⌒ —2.00 cyl., axis 160 for the left eye at this time.

External examination performed in the home at the age of 12 years revealed a mild but definite head tremor. The eyes were straight in the primary position. The ocular excursions showed overactivity of the inferior oblique muscle when he was looking up to the right or to the left. There were considerable divergence under cover and moderate nystagmoid jerking in the extremes of gaze. The pupillary reflexes were normal. Funduscopic examination showed many small, strandlike opacities of the vitreous. The disks were of good color and possessed normal capillarity. A small temporal myopic conus was seen in each eye. The macular areas showed no foveal reflexes, and there was distinct clumping of pigment granules scattered in and about the macular region. The retinal vessels were slightly smaller than normal. Nasal to the disk, both superiorly and inferiorly, the retina was distinctly atrophic, with numerous pinpoint flecks and larger aggregations of pigment. The choroidal vasculature was vividly seen but seemed to be deficient throughout, possibly as a result of the myopia. Large vortex veins were observed in the superior and inferior nasal periphery. Migratory pigment had outlined a few of the smaller peripheral vessels of the retina. The superior temporal portion of the retina was likewise atrophic, but here the pigment clumping assumed the more typical bone corpuscular, or lattice-like, pattern. A few scattered, dull gray verrucae were seen in the extreme periphery. The inferior temporal portion of the periphery was less atrophic but likewise showed unmistakable evidence of degeneration. The fundi were quite similar in appearance, but the pathologic process seemed to be more advanced in the right eye. In the con-

frontation test the fields showed extreme contraction. With a —8.00 sphere for the right eye and a —9.00 sphere for the left, corrected vision was 6/12 —1 and 6/15 +1, respectively. Color vision was normal (Ishihara).

25-1.—J. Ch., a blond, slender boy aged 13, had noticed a visual handicap, which seemed to be getting severer and was more apparent at dusk. His teacher had requested an ocular examination when he was only 7 years of age. Through the courtesy of A. N. Abbott, D.O., we learned that in September 1945 the refractive error was + 2.00 sph. ⊃ — 3.00 cyl., axis 180 in each eye and that the corrected visual acuity was 20/20 in each eye. With the same correction, vision in July 1947 was 20/30 in the right eye and 20/25 in the left eye.

Our examination in September 1946 (at the age of 13) revealed a grossly normal external condition. The irides were blue, with much gold and brown around the pupillary margin. The central media were normal. The optic nerve heads were normal except for slight pallor. The macular areas were devoid of any pathologic condition, but no foveal reflex could be seen in either eye. The retinal vasculature was normal. The retinas were atrophic in the superior temporal and nasal quadrants, the pigmentary clumping assuming a linear, strandlike, interdigitating network rather than the usual bone corpuscle appearance. This retinal change encroached on the macular zone from above, and similar changes appeared in the periphery nasally and inferiorly, but were here much more remote from the central area. The temporal portion of the retina seemed to be wholly intact. The choroidal vessels were most vividly seen in the atrophic zones of the retina and did not show evidence of sclerosis. These changes were remarkably symmetric in the two eyes. Confrontation tests of the fields showed minor peripheral constriction, which was more marked superiorly in both eyes, despite the fundic picture. Color vision was normal.

31-1.—B. E. W., a 6 year old, slightly obese girl, had a visual acuity of 6/15 in each eye with the Snellen E chart. We were told that she had no visual difficulties and was doing well in school. External examination showed slight ptosis of the left lid and a minimal, but definite, epicanthus in each eye. The eyes were straight in the primary position, and there was minor esophoria under cover. The remainder of the external examination was noncontributory. Funduscopic study showed a nearly complete pigment ring about the optic disk in each retina. The optic nerve heads and the retinal vessels were normal. There were numerous glistening, yellow, verruciform deposits about the disks and macular areas. These deposits were present elsewhere throughout the fundus but were less numerous in the periphery. The fundi of this girl showed less pigment than did those of the other affected women studied, and the choroidal vasculature was vividly seen. No other pathologic changes were noted. The fields were normal in the confrontation test. Color vision was normal on the Ishihara line charts.

32-1.—J. L. P., a well developed 4 year old girl, had uncorrected visual acuity of approximately 6/15 in each eye with the Snellen E chart. The child had no specific ocular complaints, and the parents denied that there was evidence of night blindness. External ocular examination revealed no pathologic condition. The funduscopic examination also showed a normal condition except for the presence of yellow, glistening verrucae scattered throughout the entire fundus except in the central macular areas. As in most children of this age, the peripheral retinal pigment was somewhat sparse. This girl showed less manifestation of the tapetal-like reflex of the fundus than did any of the other female patients. Retinoscopic examination, performed with paredrine and atropine cycloplegia, gave the following correction: right eye: + 1.25 sph. ⊃ 0.0; left eye: +1.25 sph. ⊃ + 0.37 cyl., axis 178. Color vision was not tested.

32-2.—J. E. P., a somewhat anemic-appearing girl, aged 2½ years, was first seen on Sept. 8, 1947. The parents stated that she started to walk later than normal and was continually falling over objects and bumping into furniture. It was impossible to determine the degree of visual acuity, but it was evidently poor. The eyes were straight in the primary position, but there was marked lateral deviation under cover, which at times was sufficiently pronounced to be considered an incipient divergent strabismus. Funduscopic examination showed a few vitreous opacities in each eye. The disks were large and oval horizontally and of normal color and capillarity. A small inferior temporal retinal conus was present in each eye. The fundi were those of a blonde person, with the associated myopic changes. The choroidal circulation was prominent, and the vasculature seemed sparse. There was a conspicuous paucity of retinal pigment, but no abnormality was seen. An extensive distribution of minute, glistening gold bodies was seen extending from the macula to the periphery in each fundus. At first these were difficult to see, owing to the poorly developed pigmentary background in these fundi. Refraction with paredrine and atropine cycloplegia revealed the following errors: right eye: —9.50 sph. ⌒ —0.25 cyl., axis 5; left eye: —9.50 sph. ⌒ —2.00 cyl., axis 180. With this correction, the child was reported to be getting about the house with less difficulty. Fields were difficult to determine by confrontation, but we were unable to detect any specific defects. Color vision was not tested.

MODE OF INHERITANCE

The distribution of cases of retinitis pigmentosa and tapetal reflex in the pedigree (fig. 1) obviously suggests the presence of a sex-linked gene producing both abnormalities. The affected males are in all cases sons of mothers having the tapetal trait. On the assumption of a sex-linked factor which produces retinitis pigmentosa in males and the tapetum-like fundus in heterozygous females, we should expect equal numbers of affected and normal children among both sons and daughters of women showing the tapetal trait. Among children of affected males, however, all daughters, but no sons, would be expected to be affected. The observed frequencies found by pooling the children of such families (table 1) are in obvious agreement with these expectations. The propositus (*12-1*) and his mother (*3-9*) are omitted in tallying the children of sibships *12* and *3*, since these sibships were ascertained through these affected members. Sibship *3* is listed separately, since the mother is not actually known to have possessed the tapetum-like fundi.

In the last two columns of table 1, the total numbers of sons and daughters are compared, such totals including unexamined as well as examined children. Among the children of affected females, the ratio of sons to daughters is 12:18, a deviation in the direction expected if prenatal death occurred in some of the males inheriting the pathologic gene. However, the deviation is not statistically significant, nor does the ratio of 3 normal sons to 3 affected sons among the children examined tend to support the assumption of reduced viability of affected males.

As with all pedigrees suggesting sex linkage, one must consider an alternative genetic hypothesis, namely, that of an autosomal gene pro-

ducing different phenotypes in the two sexes. According to this hypothesis, affected males would produce affected sons and normal daughters with a total probability equal to that for normal sons and affected daughters. In the two sibships supplying information on this point, namely, *6* and *32*, there occurred no affected sons or normal daughters among 5 children examined. The probability of this event is $\frac{1}{32}$, a figure which constitutes significant evidence against the hypothesis of autosomal inheritance.

One may also consider the possibility of a partially sex-linked gene [4] having different manifestations in the two sexes. The father (*1-2*) of sibship *3* had a history of progressive blindness, and, although the few available facts do not suggest the presence of the disease found in his descendants, he may for the moment be considered to have been affected. His children would then best be explained by assuming him to be heterozygous for a partially sex-linked gene, the abnormal gene being

TABLE 1.—*Frequencies of Normal and Affected Children of Affected Males and Females*

Children of:	Affected Sons	Normal Sons	Affected Daughters	Normal Daughters	Total Sons	Total Daughters
2-3 (presumably affected female).	1	1	4*	1	4	8
Affected females...	2†	2	4	6	8	10
Affected males.....	0	2	3	0	4	4

* The mother of the propositus, 3-9, is omitted.
† The propositus, 12-1, is omitted.

on the paired portion of his x-chromosome. One would then have to count *3-1* and *3-2* as representing cross-overs and the remaining 6 examined children non-cross-overs. However, having crossed over to the y-chromosome, the gene in *3-2* would now be expected to pass preferentially to sons; hence, the data on sibship *6* would require the postulation of 3 cross-overs, an improbable result. Ordinary sex-linkage, with the gene located in the unpaired portion of the x-chromosome, appears to be a much more probable explanation.

The fact that the sex-linked gene producing retinitis pigmentosa in this family is incompletely recessive, i. e., produces an observable effect in heterozygotes, is not unusual. Levit [5] found this to be true of the majority of human sex-linked abnormalities known in 1936, and additional examples have since been reported.[6] Red-green color blindness

4. Haldane, J. B. S.: A Search for Incomplete Sex-Linkage in Man, Ann. Eugenics **7**:28-57, 1936.

5. Levit, S. G.: The Problem of Dominance in Man, J. Genet. **33**:411-434, 1936.

6. Rundles, R. W., and Malls, H. F.: Hereditary (? Sex-Linked) Anemia, Am. J. Med. Sc. **211**:641-58, 1946. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, p. 1518.

and hereditary optic atrophy are examples of sex-linked ocular anomalies which are frequently manifested in heterozygous women. Choroideremia has recently been shown to belong to this group and will be discussed more fully later. Still other ocular anomalies showing this mode of inheritance have been studied at the Heredity Clinic and will be reported in subsequent articles.

COLOR VISION

All persons examined in this study, with the exception of young children, were tested for defects in color vision by means of Ishihara plates. Such tests seemed particularly desirable in the study of this kindred, since the commoner forms of "color blindness" are sex linked and the opportunity to investigate the cross-over frequency between

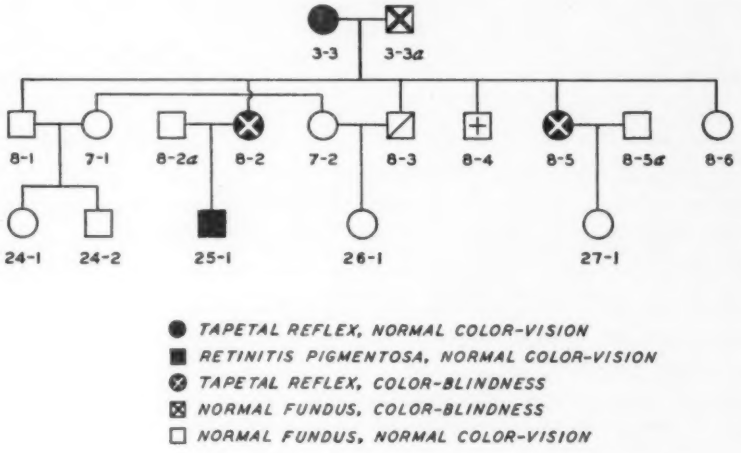

Fig. 3.—Pedigree chart showing color blindness in 2 sisters with tapetal-like reflex and their color-blind father.

retinitis pigmentosa and color blindness might therefore be presented. Of 30 males and 34 females tested, only 3 cases of defective color vision were encountered, but these happened to be strategically situated and of unusual interest. The cases were those of 2 sisters with the tapetum-like fundi, *8-2* and *8-5*, and their color blind father, *3-3a* (fig. 3). The anomaly, in so far as can be judged from the Ishihara test, was very similar in these 3 subjects, but the responses differed from those which are characteristic of deuteranopia or deuteranomaly (table 2).

Assuming that the gene responsible for this form of color blindness is sex linked, it is evident that *8-2* and *8-5* are only heterozygous for it, since *8-2* has produced a son with normal color vision. Moreover, to be homozygous, *8-2* and *8-5* would have had to receive the factor from *3-3*, an event rendered improbable by the

absence of color blindness among her many collateral relatives. Now, occasional defective color vision in heterozygous females is not unusual. But the question then arises why the third daughter of *3-3a*, namely *8-6*, being likewise, by hypothesis, heterozygous, is not color blind. The fact that she alone of the 3 daughters failed to inherit the tapetum-like fundus suggests that a form of interaction of these two genes may have produced color blindness in her sisters. Chance association cannot, however, be excluded.

Since *8-2* and *8-5* have inherited the two abnormal genes on different x-chromosomes, we may count *25-1* as representing a non-cross-over, since he possesses retinitis pigmentosa without color blindness. The daughter of *8-5* failed to inherit the tapetal character and has also

TABLE 2.—*Test Responses to Color Vision Plates**

Observer	Sex	Plate Number																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
3-3	♀	12	8	6	29	57	5	3	15	24	2	6	97	45	5	7	16	23	..	..	..	..	26	42	35	96
3-3a	♂	12	..	..	..	27	..	8	15	74	..	6	..	..	..	7	16	..	..	..	..	..	2	4	3	9
8-1	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-2	♀	12	3	6	20	..	2	3	17	21	..	..	..	..	..	..	..	..	..	..	..	..	2	4	3	9
8-5	♀	12	8	6	20	33	2	5	13	21	..	6	..	..	..	9	..	..	..	..	..	..	2	4	3	9
8-6	♀	12	8	6	29	57	5	8	15	71	2	6	87	45	9	7	16	23	..	..	..	..	26	42	35	96
7-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
24-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
24-2	♂	12	8	6	29	57	5	8	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-2a	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
25-1	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
7-2	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
26-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-5a	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
27-1	♀	Normal on plates 26, 27, 28 and 32																							

* The plates in the Ishihara "Tests for Colour-Blindness," seventh edition (Tokyo, Kanehara, 1936).

normal color vision; but, in view of the variation shown by *8-2, 8-5* and *8-6,* we cannot definitely conclude that *27-1* lacks the gene for color blindness, and we must therefore consider her indeterminate with respect to crossing over.

COMMENT

Retinitis pigmentosa is well known for its diversity of clinical manifestations, and, as might therefore be expected, the genetics of this disease suggests that it may result from many different genotypes. In addition to (1) autosomal recessive inheritance, which appears to account for the majority of cases, there have been described numerous pedigrees showing (2) dominant autosomal inheritance and a few showing (3) sex-linked recessive inheritance. Furthermore, Haldane [4] has shown that some of the pedigrees formerly attributed to autosomal dominant or recessive genes are more probably due to genes located in the paired portions of the x- and v-chromosomes. We may thus

add (4) dominant partial sex linkage and (5) recessive partial sex linkage to the possible modes of inheritance of retinitis pigmentosa. In addition, retinitis pigmentosa is observed in at least two well known genetic syndromes, namely, the syndrome of Laurence-Moon-Bardet-Biedl (retinitis pigmentosa, polydactyly, obesity and hypogenitalism) and the juvenile form of amaurotic idiocy. Finally, there are a number of allied abiotrophies of the retina and choroid which sometimes show their relation to retinitis pigmentosa by replacing or antedating the latter condition in a given patient or by occurring in other members of the same kindred. Included in the latter group are retinitis pigmentosa sine pigmento, retinitis punctata albescens, atrophia gyrata choroideae et retinae, choroideremia and night blindness.

Of particular interest to the present discussion are the sex-linked forms of choroidoretinal degeneration. Pedigrees of sex-linked retinitis pigmentosa are scarce. In her extensive (1922) compilation of 297 published family histories, Bell[7] presented but one pedigree with definite indication of sex linkage, this being a kindred studied by Nettleship and later investigated more extensively by Usher.[8] All members examined by Usher were males who exhibited myopia of 2 to 8 D.; heterozygous women regularly showed myopia without retinitis pigmentosa. Additional pedigrees of sex-linked retinitis pigmentosa have been described by Gasalla,[9] Seggel,[10] Frazer,[10] McQuarrie[11] and Allan.[12] None of these authors reported funduscopic changes in any female members of their families. This raises the question whether the kindred described in this paper differs in this respect from other pedigrees of the sex-linked trait, or whether previous authors have merely failed to note the minor funduscopic changes in heterozygous women.

Another possibility is that the disease in the present family is actually an example of one of the several variants of retinitis pigmentosa. Choroideremia (so-called) is of particular interest in this respect, for several reasons. It has been found to occur almost exclusively in

7. Bell, J.: Retinitis Pigmentosa and Allied Diseases, in Treasury of Human Inheritance (Galton Laboratory, University of London), 1922, vol. 2, plates i-xxvi, pp. 1-123.

8. Usher, C. H.: On a Few Hereditary Eye Affections, Tr. Ophth. Soc. United Kingdom **55**:164-245, 1935.

9. Gasalla, M. L.: L'hérédité dans une famille attiente de rétinite pigmentaire, Bull. et mém. Soc. franç. d'opht. **44**:169-73, 1931.

10. Seggel and Frazer, cited by Usher.[8]

11. McQuarrie, M. D.: Two Pedigrees of Hereditary Blindness in Man, J. Genet. **30**:147-53, 1935.

12. Allan, W.: Eugenic Significance of Retinitis Pigmentosa, Arch. Ophth. **18**:938-947 (Dec.) 1939.

males. Mauthner,[13] Koenig [14] and Wolf [15] each described the condition in brothers. More extensive genetic studies by Smith and Usher,[16] Zorn,[17] Schutzbach,[18] Goedblad [19] and Waardenburg [20] have shown the disease to be sex linked. Goedblad, in particular, emphasized the fact that heterozygous females regularly show a "salt and pepper" appearance of the fundus. McCullough and McCullough [21] recently confirmed this mode of inheritance in two large American families. Heterozygous females are described as having a combination of pigmentative and depigmentative changes in the fundi, occurring chiefly in the midperiphery. Small, irregular or squarish accumulations of pigment are interspersed with pale or yellowish areas of depigmentation, which radiate in irregular bands toward the ora serrata. This abnormality of the fundus was invariably present in genetically ascertained carriers. It appeared to be constant with age and was unaccompanied with any detectable changes in vision.

Niccol [3] described a brother and sister with large oval defects of the choroid at the macula in each eye, unaccompanied with mental defect or skeletal changes. The parents were unrelated, but in the mother's eyes the maculas were "stippled with light yellow specks like gold dust, lying deeper than the retinal vessels and not definitely related to them in distribution—what appears to be an example of tapetal reflex."

Gyrate atrophy of the choroid and retina is another condition resembling retinitis pigmentosa, and it has been reported to occur in families which also contain cases of retinitis pigmentosa or choroideremia. Waardenburg [22] described a sex-linked recessive pedigree of gyrate

13. Mauthner, L.: Ein Fall von Choroideremie, Ber. d. Naturw.-med. Verein in Innsbruck **2**:191-197, 1871-1872.

14. Koenig, H.: Zwei Beobachtungen von mangelhafter Entwickelung der Choroidea verbunden mit Hemeralopie, Inaug. Dissert., Griefswald, 1874.

15. Wolf, S.: Choroideremia, Arch. Ophth. **3**:80-87 (Jan.) 1930.

16. Smith, H. E., and Usher, C. H.: Choroideremia and Two Other Varieties of Night Blindness in the Same Pedigree, Roy. London Ophth. Hosp. Rep. **26**:157-174, 1916.

17. Zorn, B.: Ueber familäre atypische Pigmentdegeneration der Netzhaut (totale Aderhautatrophie), Arch. f. Ophth. **101**:1-13, 1920.

18. Schutzbach, M.: Ueber erbliche Aderhaut-Netzhauterkrankung, Arch. f. Ophth. **138**:315-331, 1938.

19. Goedblad, J.: Mode of Inheritance of Choroideremia, Ophthalmologica **194**:308-315, 1942.

20. Waardenburg, P. J.: Choroideremie als Erbmerkmal, Acta ophth. **20**:235-274, 1942.

21. McCullough, C., and McCullough, R. J. P.: A Hereditary and Clinical Study of Choroideremia, Tr. Am. Acad. Ophth. **52**:160-190, 1948.

22. Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, The Hague, Nijhoff, 1932.

atrophy but did not mention any funduscopic peculiarities of heterozygotes.

On the basis of the aforementioned facts, some authors have suggested that retinitis pigmentosa, choroideremia, gyrate atrophy and congenital night blindness are all stages of the same disease process. Inasmuch as sex-linked inheritance has been observed in certain cases of all these diseases, a unitarian concept would perhaps seem more attractive if restricted to the sex-linked forms of choroidoretinal degeneration. However, even here the available facts are too few to warrant the assumption of a single sex-linked gene or a common mode of pathogenesis. With regard to the present family, a definite classification of the pathologic changes is impossible. At present, the fundus picture in the 3 males examined most closely resembled retinitis pigmentosa, but it is quite possible that the picture of "choroideremia" might supervene at a later date. That the present disease may be somewhat distinct, however, is perhaps best suggested by the funduscopic appearances in carrier females. In three large kindreds showing sex-linked choroidoretinal degeneration, we have observed distinct differences in the abnormalities in the fundi of heterozygous women. In one family, the males show fundi typical of "choroideremia," and heterozygous females show minor pigmentative changes, like those described by Schutzbach and the McCulloughs. In a second family—the present one—the fundi of males are more typical of retinitis pigmentosa, while those of females show the golden granular change which we have described as a "tapetal reflex." In a third family, males, again, have fairly typical retinitis pigmentosa or retinitis punctata albescens, but none of the heterozygotes show detectable abnormalities of the fundus. In view of the uniformity within kindreds, we feel that the variations are probably not due to modifying genes acting on the same sex-linked gene, but that different sex-linked genes are probably present in these families. They could, of course, be allelic mutations, and they might also have very similar mechanisms of pathogenesis.

SIGNIFICANCE OF THE TAPETUM-LIKE FUNDUS

Observing the abnormal fundi of the 2 women originally seen in this study, one of us (H. F. F.) was led to describe the anomaly as a "tapetal reflex," since the picture reminded him of the cases described by Mann.[1] It is possible that this appearance is identical with or similar to that described in carriers of "choroideremia." However, having made the analogy with a tapetum, we were led to further comparisons in the literature, which it may be of interest to relate here. Mann observed that the fundi of her 2 women most nearly resembled the patchy golden fundus of the galago, a nocturnal lemuroid primate. This is interesting, since it is known [23] that a tapetum lucidum is found

23. Walls, G. L.: The Vertebrate Eye, Bloomfield Hills, Mich., Cranbrook Press, 1942.

among primates only in night monkeys of the genus Aotus and in two lemuroid genera, Galago and Loris. Regarding the two latter, Johnson [24] wrote in 1901:

> I have noticed in certain night animals, more particularly in the Galagos and Lorides, a heaping-up of pigment all around the periphery, which, seen with the ophthalmoscope, greatly resembles Retinitis pigmentosa. Exposing a Galago to daylight for some months, I found it to go quite blind; the invasion of the pigment could clearly be seen to advance concentrically towards the posterior pole, as I have seen the disease spread in Man . . . I thought that these observations on night animals pointed to the possibility of arresting the insidious progress of the disease, of which blindness is the invariable termination, by shielding the eyes from the most active rays of daylight. A few attempts to do this by the use of spectrum-blue goggles . . . have given encouraging results, and I am therefore persevering in that direction.

Similar observations on galagos have been made by Hardy,[25] and it is interesting that Dr. Johnson's analogy is now reenforced by the knowledge that at least one form of retinitis pigmentosa in man has a heterozygous manifestation which simulates the fundus of a normal galago. The possibility that some forms of primary retinal degeneration may be dependent on an abnormal photochemical reaction of the neuroepithelium has been suggested by others. Leber [26] proposed this view and called attention to the fact that other hereditary diseases are known in which the action of an abnormal gene is evidently potentiated by light, e. g., xeroderma pigmentosum and congenital porphyrinuria. Embryologic studies by Bourne and others (cf. Grüneberg [27]) in a strain of rat possessing an inherited pigmentary degeneration of the retina have shown that retinal development is apparently normal up to the time the eyes open, whereupon degenerative changes almost immediately set in.

In citing the foregoing references, it is our purpose only to call attention to an etiologic theory which would seem to merit further investigation. Regarding the pathologic significance of the tapetal-like change in the fundus seen in the present family, little can be said except that we are inclined to regard this abnormality as a forerunner of a more extensive change in the choroid or retina, which leads to retinal degeneration in males. According to this view, one would perhaps expect to observe the abnormality at an early age in males, but no opportunity to investigate this point was offered in this study, since

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24. Johnson, G. L.: Contributions to the Comparative Anatomy of the Mammalian Eye, Chiefly Based on Ophthalmoscopic Examination [plates 1-30], Phil. Tr. Roy. Soc. London, s. B **194**:1-82, 1901.

25. Hardy, L.: Personal communication to the authors, 1947.

26. Leber, T.: Die Krankheiten der Netzhaut, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1916, vol. 7, pt. 2, p. 1222.

27. Grüneberg, H.: Animal Genetics and Medicine, New York, Paul B. Hoeber, Inc., 1947.

none of the heterozygous women had sons younger than 10 years of age. At the ages of 12, 13 and 30 years, none of the affected males in this family showed the golden granular change in any portion of the fundus. In families with choroideremia, the typical female fundus was found in young males by the McCulloughs.[21] These authors suggested that the heterozygous change in the fundus in persons with choroideremia is probably a stationary anomaly. There is some suggestion in our family that the abnormality may be a slowly progressive one in females, but much more careful study would be needed to establish this. Whereas the McCulloughs asserted that the areas of depigmentation in the fundi of carriers of choroideremia are probably due to thinning of the choroid and visualization of the sclera, we have interpreted the golden granules seen in the carriers in our family as evidence of hyperplastic change, perhaps, as suggested by Mann,[1] thickenings or verrucae in the lamina vitrea (lamina basalis).

The practical significance of the tapetum-like fundus is apparent. By the presence or absence of this anomaly one may distinguish, in a family possessing sex-linked retinitis pigmentosa, those females capable of transmitting the disease from those who are not. Thus, in the present family, those females (viz., *3-3, 3-8, 3-10, 3-11, 8-5, 11-2, 31-1, 32-1* and *32-2*) who exhibit the tapetal-like reflex but have not yet produced children, or, having children, have not yet produced sons with retinitis pigmentosa, have been warned concerning this possibility. On the other hand, those females who but for the absence of this fundic picture might also have been suspected of being carriers (viz., *8-6, 11-3, 13-1, 13-2, 22-1, 27-1* and numerous descendants of *3-1*) can be assured that they have little or no chance of producing blind sons.

The practicing ophthalmologist will seldom be able to examine a large number of relatives of his parents. However, on the basis of this study and other recent reports, it would seem definitely advisable for him to examine carefully all the close relatives of patients having retinitis pigmentosa or related conditions, even though all these relatives are reported to have good visual acuity. If, for example, a male patient with retinitis pigmentosa has what appears to be a negative family history for the disease, one might suspect that the responsible genetic factor is an autosomal recessive. However, the finding of a tapetum-like fundus or similar abnormality in this patient's mother, or in a sister or daughter, would strongly suggest the presence of a sex-linked form of choroidoretinal degeneration. This would considerably alter one's predictions concerning the likelihood of defective children and grandchildren. Further study of the carriers of such sex-linked genes by clinical, biochemical and, when possible, histologic methods would also undoubtedly add greatly to our understanding of this important group of diseases.

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A METHOD OF PRESERVATION OF ANIMAL EYES

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BY PRACTICE on animal eyes interns and residents in ophthalmology acquire skill, familiarity, confidence and courage in handling their instruments and in executing the standard surgical maneuvers. Large numbers of animal eyes are needed for the teaching and examination of these students and for investigational use in ophthalmic surgery. In some states their use is discountenanced, and it is difficult or impossible to obtain them, especially on short notice. At best, it may be difficult to procure them in sufficient quantity when wanted, because of lack of material and of men who can remove them without damage. Hence there arose the idea of finding a method of preservation so that a large number of eyes could be on hand when and where needed.

The eyes of kittens 6 to 8 weeks old are quite satisfactory if enucleated shortly after death. In most large cities they can be obtained with little trouble from societies for prevention of cruelty to animals.

The enucleation must be carefully performed. With Stevens' tenotomy scissors the lids are dissected completely away from their attachment to the orbital margin and the canthal ligaments. The conjunctiva is then grasped as close to the orbital wall as possible, and the dissection is carried out by slight traction on the globe and by keeping the scissors close to the orbital wall to avoid cutting the sclera. This technic permits removal of the muscles and the deep retrobulbar tissues with their attachments to the eyeball intact. These appendages are wanted for clamping the eye when it is used. The optic nerve is severed as far back as possible.

Chemical methods of preservation were tried but were rejected because they toughen the coats of the eye and cloud the cornea. Freezing the eyes in isotonic solution gives much better results. Quick freezing with the lids *in situ*, that is with the cornea covered and protected, was first tried, but after five or six days the eyes became unsuitable for cataract extraction and operations for glaucoma because release of the ocular pigment into the anterior chamber made it difficult or impossible to see any details. The corneas were only slightly cloudy at first but became more so if the eyes were handled the least bit roughly.

The method of preservation found most successful and now recommended is immersion and freezing of the eyes in an ice cube tray filled with Locke's solution. To keep the cornea pointed upward and approximately in the middle of the compartment, a small lead weight is attached to the appendages at the back of the globe. With Locke's solution the cornea remains clear. The eyes are frozen at a temperature of 10 F. in an ordinary refrigerator. The freezing process takes approximately one hour. No difference was found in the state of preservation of the eyes whether they were frozen rapidly or slowly. After the cubes are thoroughly frozen they can be kept for any length of time at a temperature slightly below freezing. The advantage of preserving the eye in the middle of an ice cube is that no special care need be taken in the handling, as the jacket of ice protects the eye from any trauma. When one or more eyes are required, it is necessary only to run cool water on the tray and as many cubes as desired can be removed, the rest being replaced for use later. The cool water is run on the cube until the cornea is just free from ice. The water is then run on the posterior portion of the cube until the ice jacket can be removed without causing damage. Water should not be run on the posterior portion of the cube until it is completely thawed inside, since the frozen posterior portion aids in fixing the eyes in the operating mask or other device. To suit convenience, the entire contents of the tray may be removed at one time, and the individual cubes, separated by strips of wax paper, may be replaced in the refrigerator or stored in a "deep freeze" unit at 10 F. After removal of the ice jacket, the eye becomes soft enough for use in about ten minutes when kept at room temperature.

If the eye should be too soft, clamping of the muscle cone close to the globe will readily raise the tension. The anterior chamber can be deepened as desired if a solution of fresh gelatin is introduced into it at the limbus by means of an ordinary hypodermic syringe and needle; but if care is taken in defrosting the posterior portion of the globe, this procedure is usually unnecessary. A rotary movement of the needle facilitates its entry into the chamber.

For transportation, the ice cubes containing the eyes may be packed between sheets of dry ice® (carbon dioxide snow) 1 inch (2.5 cm.) in thickness in an insulated cardboard box. Insulated cardboard boxes may be obtained from any ice cream company or any company handling dry ice.® The boxes are sealed with tape. A 1 inch linear opening is left in the top of the box to allow for the escape of carbon dioxide. If this opening were not made, the box would rupture from the accumulation of carbon dioxide. So packed, the eyes will remain frozen while in transit for three days.

SUMMARY

A method is presented of preserving and transporting animal eyes for use in the practice of ophthalmic surgery. The eyes are weighted individually with a lead bob to keep them in position and are frozen in Locke's solution as ice cubes in an ordinary refrigerator. For shipment the eyes are packed in dry ice.

NOTE.—The eyes prepared as described in this paper were used in the laboratory and found to be satisfactory by the late Dr. T. L. Terry, of Boston, and by Dr. D. B. Kirby, of New York.

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